

Review

Current status of the therapeutic uses and actions of the preferential cyclo-oxygenase-2 NSAID, nimesulide

K. D. Rainsford

Biomedical Research Centre, Sheffield Hallam University, Sheffield, S1 1WB, UK, e-mail: k.d.rainsford@shu.ac.uk

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Abstract. This review summarizes the principal therapeutic responses to the preferential COX-2 NSAID, nimesulide, in treating musculo-skeletal joint symptoms and various acute and chronic pain conditions and the mode of action in relation to therapy in these states.

In extensive studies in laboratory animal models and clinical trials in patients nimesulide has been found to have potent analgesic, anti-inflammatory and anti-pyretic activities. It is approved for use in over 50 countries worldwide (including those in the EU, South and Central America, China, India and some other South-East Asia) for the treatment of acute pain, the symptomatic treatment of painful osteoarthritis and primary dysmenorrhoea. Its mode of action in these states is related to the preferential inhibition of the production of cyclo-oxygenase-2 (COX-2) and other inflammatory mediators whose production is controlled by stimulation of cyclic-3',5'-adenosine monophosphate (cAMP); this means that nimesulide is a multi-factorial drug in controlling inflammation and pain.

The adverse reaction profile of nimesulide is, in general, like that of other NSAIDs. It does, however, have relatively low occurrence of gastro-intestinal (GI) side effects which is related to its low propensity to inhibit the physiologically important COX-1 in the GI mucosa and important physico-chemical properties (high pKa of 6.5 and lipophilicity) as well as inhibiting of mast cell derived histamine and acid secretion in the stomach. In contrast with the coxibs, nimesulide has not been found to have appreciable cardiovascular toxicity.

Key words: NSAID; Anti-inflammatory; Analgesic; Side-effects; Sulphonanilide; Cyclooxygenase

Introduction

It is well-established that non-steroidal anti-inflammatory drugs (NSAIDs) have fundamental actions in controlling inflammation and in pain relief (Kean and Buchanan, 2005). They all inhibit the production of prostaglandins through the inhibition of COX-1 and COX-2, these being the enzymes responsible for their synthesis (Vane and Botting, 2001; Rainsford, 2004a). In addition, however studies in experimental and clinical models have clearly demonstrated other activities on pro-inflammatory mediators involved in the actions of NSAIDs in providing relief from inflammation and pain (Kitchen et al., 1985; Hunneyball et al., 1989; Rainsford, 1996; Celotti and Laufer, 2001; Tarnawski and Jones, 2003; Rainsford, 2004.). Among these mechanisms are the inhibition of leucocyte accumulation at inflamed sites, activation and expression of cell surface receptors, of angiogenesis, cell apoptosis, reactive oxygen species (ROS, or oxyradicals and nitric oxide) and their actions, and the regulation of non-prostanoid lipid mediators (Kitchen et al., 1985; Hunneyball et al., 1989; Rainsford, 1996; Tarnawski and Jones, 2003; Rainsford 2004a, 2004b; Celotti and Laufer, 2001; Serhan, 2004).

Aside from individual variations in pharmacological effects NSAIDs also differ substantially in the pharmacokinetic, pharmacological, pharmacodynamic and in their clinical profiles (Hart and Huskisson, 1984; Brogden, 1986; Banwarth et al., 1989; Levy and Smith, 1989; Netter et al., 1993; Evans, 1996; Hayball, 1996; Rainsford, 1996; Lefkowith 1999; Heyneman et al., 2000; Verbeeck 1990; Celotti and Laufer, 2001; Day 2001; Landoni and Scoraci, 2001; Bijlsma 2002; Tarnawski and Jones, 2003; Rainsford et al., 2005a, 2005b; Huntjens et al., 2005). Since they have essentially the same therapeutic properties in controlling pain, inflammation and fever, the scale of adverse effects often remains the main discriminator for choosing between individual NSAID (Hart and Huskisson, 1984; Rainsford, 1996; Kean and Buchanan, 2005).

Gastrointestinal (GI) adverse events remain the main concern in the use of NSAIDs and GI tolerability is a central issue for clinicians who prescribe these drugs (Rainsford, 1996, 2001; Rothstein, 1998). Other important side effects should also be taken into consideration when prescribing these drugs such as allergic reactions, skin adverse reaction, renal complications, alteration of hepatic enzyme levels and rarely hepatopathies (Rainsford, 1996, 1997, 2001; Rothstein, 1998; Teoh and Farrell, 2003; Uemura et al., 2003; Simon and Namazy, 2003; Sanchez-Borges et al., 2002, 2003; McGettigan et al., 2000).

Finally, the recent withdrawal of two of the newer COX-2 selective NSAIDs, rofecoxib and valdecoxib because of serious cardiovascular reactions (the latter also due to serious skin reactions), as well as the withdrawal or limitations on the use of celecoxib in some countries poses question about the cardiovascular (CV) safety profile of the whole NSAIDs class (Rainsford, 2005c; Khanna et al., 2005; Oster and Hazleman, 2005; Topol, 2004; US Food and Drug Administration, Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Committee, 2005a; US Food and Drug Administration FDA Public Health Advisory, 2005b; European Medicines Agency, 2005a, 2005b). The FDA and EMEA took different positions on this issue. The FDA took the view that the issue concerning the CV risks of coxibs raised concerns about the CV safety of all NSAIDs (US Food and Drug Administration FDA Public Health Advisory, 2005b; European Medicines Agency, 2005a, 2005b). In contrast, the EMA considered the CV risk of coxibs was clearly greater than that of other NSAIDs whether preferential or non-selective COX-2 inhibitors (which they grouped as non-selective COX-2 inhibitors) (European Medicines Agency, 2005a, 2005b).

Traditional NSAIDs and selective COX-2 inhibitors

In 1971, Professor Sir John Vane and colleagues postulated that aspirin and other NSAIDs, produced their anti-inflammatory and analgesic effects by inhibiting the biosynthesis of prostaglandins, through the blockade of the COX enzyme (Vane, 1971; Ferreira et al., 1971; Flower et al., 1972). In the early 1990's, it became evident that two isoforms of the COX enzyme were actually involved in the production of prostaglandins (Rainsford, 2004a, Vane and Botting, 1995, 2001). In particular, it was showed that the COX-1 isoform is responsible for the production of prostaglandins which contribute to maintain the homeostasis in key organs such as the stomach and kidney as well as influence mechanisms linked to the blood coagulation and vascular functions. The other isoform, COX-2, was found to be mainly induced by inflammatory and painful stimuli and to cause the formation of prostaglandins which play a key role in the inflammation and neural responses, although more recent research attributes a role in the maintenance of homeostasis to this isoform as well (Vane and Botting, 1995, 2001; Rainsford, 2004a).

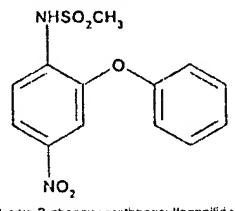
Non-selective NSAIDs inhibit both COX-1 and COX-2 by binding reversibly or irreversibly to the enzyme (Vane and Botting, 1995; Rainsford, 2004a). The toxic effects of these non-selective NSAIDs in the gastro-intestinal tract,

kidney and vascular systems are considered, in part, to be due to inhibition of the synthesis of physiologically important ("housekeeping") prostaglandins (PGs) E_2 and I_2 in these systems (Vane and Botting, 1995, 2001; Rainsford, 2004a). Inhibition of COX-2 selectively inhibits the synthesis of PGE₂ and other PGs involved in inflammation and mediating neural signals in pain pathways Vane and Botting, 1995, 2001; Rainsford 2004a, 2004b; Rainsford et al., 2005). NSAIDs exhibit different degrees of selectivity in their ability to differentially block COX-1 or COX-2 (Vane and Botting, 1995, 2001; Rainsford, 2004a; Tarnawski and Jones, 2003). While there are many other factors that are involved in the development of adverse reactions (e.g. in the GI tract and kidney) the involvement of COX-1 inhibition plays a significant part (Rainsford, 1996, 2001; Hotz-Behofsits et al., 2003; Tarnawski and Jones, 2003).

In late '90s based on the assumption that the inhibition of COX-1 is the main cause of GI bleeding, a new class of highly selective COX-2 inhibitors, the so-called coxibs, were developed (de Laval et al., 2000; Vane and Botting, 2001; Rainsford, 2004a). Their purpose was to inhibit, at recommended therapeutic doses, mainly COX-2, with little if any effects on COX-1 (Vane and Botting, 2001; Rainsford, 2004a). The coxibs were, therefore, looked at as a safer alternative to traditional NSAIDs, especially their GI safety profile. Evidence from short-term studies showed that the coxibs had lower gastro-ulcerogenic effects in animals and humans (Feldman and McMahon, 2000). Since their discovery certain physicochemical properties (high pKa, lipophilicity) have been identified that may also account for their low acute GI ulcerogenicity (Rainsford, 1999a). In long-term studies in patients with arthritic conditions this was less marked and the incidence of serious GI events from coxibs proved similar to that from NSAIDs (Bjarnason and Rainsford, 2001a, 2001b; Schoenfeld, 2001; Jüni et al., 2002).

The inhibitory activity of NSAIDs towards the two COX isoforms is only one of the aspects which play a role in their analgesic and anti-inflammatory activity. Aside from the degree of selectivity toward COX isoforms, NSAIDs can be distinguished according to other characteristics such as their chemical structure, as well as their acidic and non-acidic chemical characteristics (e.g. pKa) (Rainsford, 1999a, 2004c). Their biological activities are also due to their relative effects on the production of inflammatory and pain mediators which account for their anti-inflammatory, analgesic activities (i.e. central or peripheral) antipyretic and other pharmacological properties. Physico-chemical factors are well-known to influence pharmacokinetics of NSAIDs (Graf et al., 1975; Brune et al., 1977; Netter et al., 1993) and especially the rate of GI absorption and uptake into inflamed cells or synovial tissues and cerebrospinal fluids (Netter et al., 1993; Rainsford, 1999a, 2004c; Shimizu et al., 2003; Pehourecq et al., 2004;). NSAIDs with low pKa values (e.g. carboxylic acids) have a greater tendency to be irritant to the gastric mucosa as a consequence of their selective absorption into GI mucosal cells (Brune et al., 1977; Rainsford and Brune, 1978; Rainsford et al., 1981, 1984, 1985; Hotz-Behofsits et al., 2003; Rainsford, 1999a; Sighorsson et al., 2000a, 2000b) leading to ion trapping (Brune et al., 1977; Rainsford and Brune, 1978; Rainsford et al., 1981, 1984, 1985; Sighorsson et al., 2000), as well as uptake into mitochondria and

Physicochemical properties of nimesulide



- Non-acidic NSAID, pKa 6.4
- $\geq 100\%$ unionized at acidic pH in gastric environment
- Low water solubility: 5.5mg/L (25°C)
- MWI 308.3 Da
- $\text{Log P} (\text{Octanol/Water}, \text{pH } 7.4) = 1.8$
- Hydrogen bond donors: 1
- Hydrogen bond acceptors: 6

$\left. \begin{array}{l} \text{with pKa results in high GI permeability,} \\ \text{but low gastric irritancy} \end{array} \right\}$

Fig. 1. Physico-chemical properties of nimesulide.
From Dr Alberto Bernareggi and reproduced with his permission.

uncoupling of oxidative phosphorylation (Sigthorsson et al., 2000) leading to reduction in ATP production and apoptosis (Redlak et al., 2005). These physicochemical features of NSAIDs also underlie their renal effects (Brune et al., 1977). Drugs with relatively higher pKa than the carboxylates such as nimesulide (pKa 6.5) (Fig. 1) while being well absorbed probably have a lower propensity to lead to ion trapping in mucosal cells (Rainsford, 1999a; Sigthorsson et al., 2000) and consequently are less irritant to the mucosal cells (see later section on Adverse Reactions and Relative Safety).

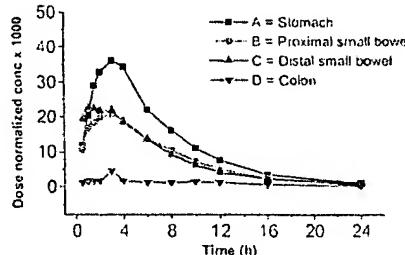
The Development of Nimesulide

Nimesulide was developed by Dr. George Moore and colleagues at Riker Laboratories (later acquired by 3M Co.) (Rainsford, 2005a). The discovery of nimesulide preceded the discovery of cyclo-oxygenase and the key roles of prostaglandins in inflammation and pain. The rationale for the design was actually based on the premise that free radicals were critical factors in chronic inflammation disease and scavenging of these radicals might have novel anti-inflammatory activities in the control of chronic inflammatory conditions (Swingle et al., 1985; Rainsford, 2005a).

Following initial unsuccessful observations on fluorokane-sulphonanilides they modified their strategy to incorporate a 4-nitro- group into the sulphonanilide structure to achieve oxyradical scavenging and this led to the synthesis of 4- nitro-2-phenoxy-trifluoromethane-sulphonanilide. The designated compound, R-805, was found to have the best therapeutic ratio compared with reference NSAIDs available at that time (Rainsford, 2005a). The chemical name of the compound, 4-nitro-2-phenoxymethane-sulphonanilide served as the basis for the generic name of the drug, i.e. nimesulide. Subsequently in 1980 nimesulide was licensed by Helsinn Healthcare SA (Switzerland) who proceeded to invest in extensive investigations on the drug. These gave a basis for comprehensive investigations that allowed for the worldwide registration and commercialisation of the drug. These studies also led to identification of the multi-factorial basis for the actions of nimesulide.

Regional absorption from GI tract

Nimesulide absorption occurs mainly in the upper part of the GI tract.



A (control leg): 100mg nimesulide dissolved in PEG400 and given in gelatine capsules. B, C, D: 100mg nimesulide given in IntelSite® capsule, with drug release in the proximal (B) and distal small bowel (C), and in the ascending colon (D).

Pharmaceutical Profiles 1999

Fig. 2. Plasma concentrations of nimesulide normalized to dose following selective introduction into different regions of the gastro-intestinal tract. These data show that about 70% of the dose of the drug taken orally is absorbed in the stomach, while about 12% is absorbed in the small bowel and virtually no absorption occurs in the colon.

Nimesulide was first licensed and marketing in Italy in 1985, over 20 years ago. Subsequently, it has become the most prescribed and used NSAID in that country. It is now marketed in over 50 countries world-wide and in some is amongst, if not, a market leader.

Mode of Action of Nimesulide

There have been several reviews published over the years on the pharmacological properties of nimesulide (Ward and Brogden, 1988; Davis and Brogden, 1994; Famaey, 1997; Anonymous, 1998; Bennett and Villa, 2000; Bennett, 2001). More recently, a monograph has been published on nimesulide which includes all the main pharmacokinetic, pharmacological, clinical and chemical properties of this drug (Rainsford, 2005b).

Pharmacokinetics

Key features of the pharmacokinetics of nimesulide, which are important in relation to its pharmacological actions, include:

- Rapid and complete absorption from the upper gastrointestinal tract (Fig. 2): peak plasma concentrations ranging from 3–6.5mg/L being reached at 1–3 h after oral ingestion of the recommended daily dose of 100 mg b.i.d. (Bernareggi, 1998; Bernareggi and Rainsford, 2005).
- Tissue distribution in rats (Fig. 3) shows rapid accumulation in fat, liver, kidney, with some uptake into brain tissue in rats. High fractional binding of the drug and its principal 4-hydroxy-metabolite to plasma proteins, principally albumin, ensures moderately low volume of distribution with $V_d/F = 0.2$ to 0.4 L/Kg (Bernareggi, 1998; Bernareggi and Rainsford, 2005a). Clearance is rapid such that most of the drug is eliminated in rats and humans by 24 h (Bernareggi, 1998; Bernareggi and Rainsford, 2005).

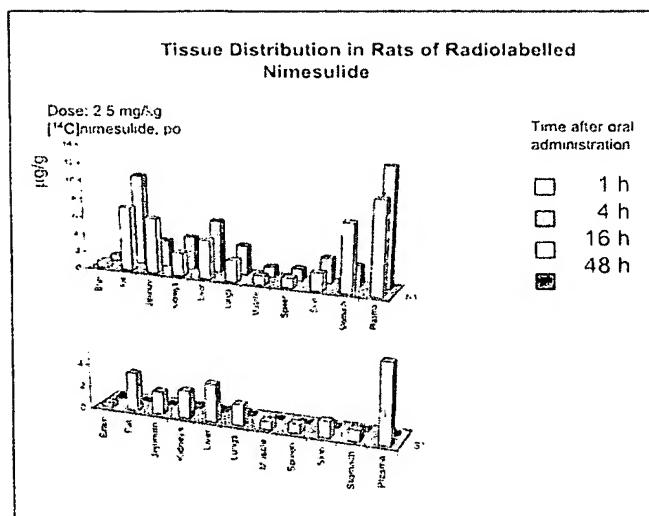


Fig. 3. Distribution in major organs of radioactive labelled-nimesulide in rats following oral administration of 2.5 mg/kg of the drug.

The upper bar graph shows the concentration ($\mu\text{g/g}$ wet weight) of nimesulide and its principle 4-hydroxy-metabolite at 1 h (front bars) and 4 h (at rear), while the bottom graph shows the concentration of these at 16 h (front bars) and 24 h (at rear) respectively.

There is widespread distribution of radioactively labelled drug within 1 h of oral administration with relatively high concentrations being present in the plasma, fat, stomach, jejunum, liver, kidneys and lungs. The presence in fat reflects the relatively high liposolubility of the drug. Although there is some uptake into the brain at 1–16 h this is not at a high level compared with the plasma concentration of the drug. The combined tissue to plasma ratio is <1 and there is no accumulation of the drug in major organs. In humans the ratios of tissue/plasma drug concentrations in synovial and genital tissues are in the range of 0.4–0.8. Figures derived from data in Table 1 and A Bernareggi et al., 2005. The position of total radioactivity and plasma levels of synovial and GI tissues in rats after intravenous and oral administration. Data on file – Helsinn Healthcare S.A.

- There is similar bioequivalence from different oral dosage forms (tablets, granules, suspension) (Bernareggi, 1998; Bernareggi and Rainsford, 2005).
- Food has a modest effect on total bioavailability; a relatively high fat American breakfast reducing peak plasma concentrations (C_{\max}) by about 20% but there is no effect on the T_{\max} or total bioavailability (AUC_{0-15hr}) (Bernareggi, 1998; Bernareggi and Rainsford, 2005).
- Liver metabolism is principally due to (a) oxidation to form hydroxylated metabolites via cytochrome P₄₅₀ 2C9, 2C19 and possibly CYP1A2, with subsequent glucuronidation and sulphation of the phenolic hydroxyl groups, and (b) reduction of the nitro-group to an amine (Bernareggi, 1998; Bernareggi and Rainsford, 2005). Nitroso- and hydroxylamine intermediates most likely occur in the reduction of the nitro-group (Bernareggi and Rainsford, 2005).

While nimesulide produces a considerable number of metabolites, the principal metabolite is the 4-hydroxy-derivative which, though generally less potent, has similar pharmacological actions to that of the parent drug (Rainsford et

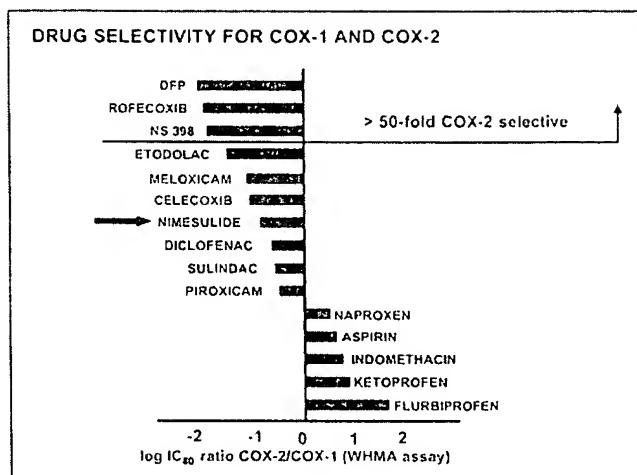


Fig. 4. *In vitro* selectivity of NSAIDs for COX-2 compared with COX-1. Based on data from Warner et al. (1999). Here there IC_{50} molar values for the inhibition of these two enzymes are compared as this is considered to give a closer representation of the likely effects in relation to the plasma concentrations of the drugs in humans.

COX-2 and anti-inflammatory activity

A large number of experimental investigations in animal models (Rainsford et al., 2005) and humans with arthritic and various pain states (Bianchi et al., 2005) have shown that nimesulide has anti-inflammatory activity which is comparable on a dose for weight basis with that of conventional NSAIDs such as diclofenac and indomethacin and the COX-2 selective drug, rofecoxib.

The effects of nimesulide, like that of other NSAIDs on COX-2 are among the mechanisms involved in the anti-inflammatory actions of this drug. The preferential COX-2 selectivity of nimesulide is a central feature of the anti-inflammatory as well as analgesic effects of this drug (Rainsford et al., 2005). Demonstration of this effect has been shown in a conventional *in vitro* and *ex vivo* assays. Among the *in vitro* assays used to define COX-1 and COX-2 selectivity of NSAIDs that developed by Warner and co-workers (Warner et al., 1999), known as the William Harvey (Institute) Modified Assay (WHMA) in whole human blood (Fig. 4) has become generally accepted to most closely represent that known to occur *in vivo* and best characterized in relation to the plasma pharmacokinetics of the drugs. The ratio of COX-2/COX-1 (which is a measure of COX-2 selectivity) in the WHMA data was found to range between diclofenac and etodolac and was close to that of celecoxib (Fig. 4). Yet the COX-2/COX-1 ratio of nimesulide is clearly out of the range of rofecoxib and NS-398, both of which are highly selective inhibitors.

To establish the significance of COX-2 selectivity in relation to GI effects and platelet function *ex vivo* studies were performed in human volunteers who had ingested either 100 mg nimesulide b.i.d. or naproxen 500 mg b.i.d. for 14 days and the COX-1/COX-2 effects were determined in blood and GI mucosa. There was no COX-1 – dependent platelet aggregation produced by nimesulide and it only

(TXA_2) and gastric mucosal production of PGE_2 and 6-keto $\text{PGF}_{1\alpha}$ in endoscopic biopsies (Bjarnason and Thjodleifsson, 1999; Sigthorsson et al., 2000a, 2000b; Shah et al., 2001). Whole blood stimulated ex vivo with *Escherichia coli* lipopolysaccharide (LPS) from the nimesulide-treated subjects produced 91–93% inhibition of PGE_2 compared with control values after 3–10 days treatment.

In comparison, the ingestion of naproxen 500 mg b.i.d. for 14 days caused significant reduction in serum TxB_2 production (by 98% of initial control values), gastric mucosal PG production by 76–82%, and blocked COX-1 dependent platelet aggregation. The LPS-stimulated whole blood PGE_2 production was significantly reduced by 74–77% of control values over 3–10 days ex vivo; the latter being less than that observed with nimesulide (Bjarnason and Thjodleifsson, 1999; Sigthorsson et al., 2000; Shah et al., 2001).

The significance of these observations on COX-2 preferential effects of nimesulide on the gastro-intestinal (GI) effects of the drug were shown in upper GI endoscopic observations performed in the same volunteers and parallel studies of intestinal permeability using specific biomarkers. In both studies nimesulide had little or no effects on the Lanza scores of gastro-duodenal mucosa or intestinal permeability whereas naproxen produced significant gastric injury (44% of subjects showing >10 erosions or haemorrhagic areas) and increased intestinal permeability. Furthermore, naproxen caused a significant two-fold increase in excretion of faecal calprotectin (a marker of intestinal inflammation) above baseline whereas nimesulide was without significant effects on the excretion of this biomarker (Bjarnason and Thjodleifsson, 1999; Sigthorsson et al., 2000; Shah et al., 2001).

These results represented the first conclusive evidence of COX-2 selectivity of an NSAID being paralleled in humans by lack of significant effects on GI mucosal integrity. These observations are supported by a large amount of studies in laboratory animal models (Sigthorsson et al., 2000) (reviewed – see Bjarnason et al., 2005; Rainsford et al., 2005) showing little or no effects of nimesulide on GI mucosal production of prostaglandins coincident with low GI mucosal injury from this drug.

Several actions of nimesulide may also account for the low GI ulcerogenicity of the drug aside from sparing of COX-1 activity in the mucosa and physico-chemical properties of the drug that limit its accumulation in mucosal cells (Bjarnasson et al., 2005). Among these actions are the effects on mast cell degranulation and release of histamine, and inhibition of histamine stimulated acid production which maybe a consequence of elevation of cyclic 3'5'-AMP by nimesulide (Bjarnasson et al., 2005) (see later). The lack of stress-synergy in expression of irritant actions of the drug on the gastric mucosa, such as seen with other NSAIDs may also be a factor of significance in the low ulcerogenicity of nimesulide (Rainsford, 1975, 1977).

The pharmacological profile of nimesulide with particular reference to its inhibitory activity on the COX enzymes, has been evaluated in various *in vitro* models. Although results vary depending on study conditions, nimesulide showed a higher affinity for the COX-2 enzyme (Rainsford et al., 2005). This is also supported by molecular modelling studies which showed that blockade of COX-2 is due to the

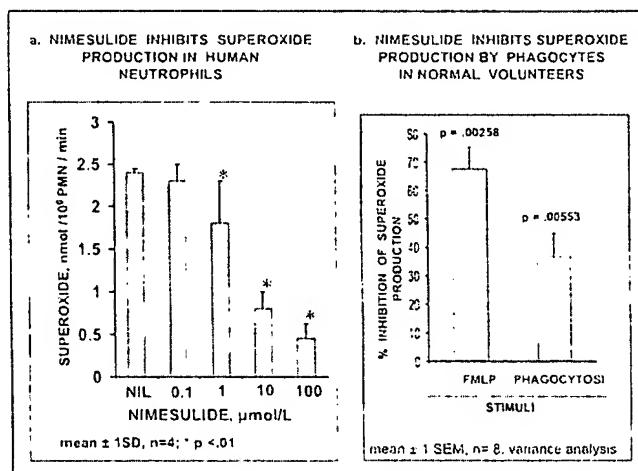


Fig. 5. Actions of nimesulide on neutrophil reactive oxygen species (ROS). Effects of nimesulide on superoxide production by human neutrophils *in vitro* (a) and on superoxide and phagocytosis by neutrophils ex vivo following ingestion by human volunteers of 100 mg nimesulide (b).

a. Based on data from Bevilacqua et al. (1994)

b. Based on data from Ottone et al. (1992)

interaction of nimesulide with the larger channel in COX-2 compared with COX-1 (Rainsford et al., 2005). In these experimental models nimesulide was also found to have some weak inhibitory activity on the COX-1 isoform (Rainsford et al., 2005), which might have therapeutic advantages in relation to prevention of thrombosis in patients with atherosclerosis.

Nimesulide, like some classical NSAIDs exhibits a considerable degree of anti-inflammatory activity as a consequence of various inhibitory effects on polymorphonuclear neutrophil leucocytes (PMNs) (Dallegr et al., 1990, 1992a, 1992b, 1995; Ottone et al., 1992, 1993, 1995, 1999; Capelli et al., 1993; Verhoeven et al., 1993; Bevilacqua et al., 1994; Dapino et al., 1994; Tool and Verhoeven, 1995; Bennett and Villa, 2000; Bennett, 2001; Mouithys-Mickalad et al., 2000; Nakatani et al., 2001; Gomez-Gavirio et al., 2002; Bravo-Cuellar et al., 2003; Kimura et al., 2003; Rainsford et al., 2005). These effects are, in some cases, relatively potent compared with the activities of other NSAIDs, and occur within the drug concentrations in plasma or synovial fluids encountered during therapy with the drug (Rainsford et al., 2005; Bennett and Villa, 2000; Bennett, 2001). Thus, nimesulide inhibits chemotaxis and superoxide production at $\geq 1 \mu\text{mol/L}$ (Fig. 5) and production of platelet activating factor, leukotriene B₄ and hypochlorous acid (HOCl) from PMNs at $\geq 10 \mu\text{mol/L}$ in concentrated-related manner (Dallegr et al., 1990, 1992a, 1995; Ottone et al., 1992, 1993, 1995; Verhoeven et al., 1993; Bennett and Villa, 2000; Bennett, 2001). At $\geq 5 \mu\text{mol/L}$ nimesulide inhibits release of elastase and other markers of neutrophil degranulation that contribute to cartilage destruction in osteoarthritis (OA) and related conditions (Ottone et al., 1993; Nakatani et al., 2001). At higher "supra-therapeutic" concentrations ($\geq 20 \mu\text{mol/L}$) nimesulide inhibits neutrophil adherence to endothelial cells, shedding of L-selectin and transendothelial migration (Fig. 6) (Dapino et al., 1994; Gomez-Gavirio et al., 2002).

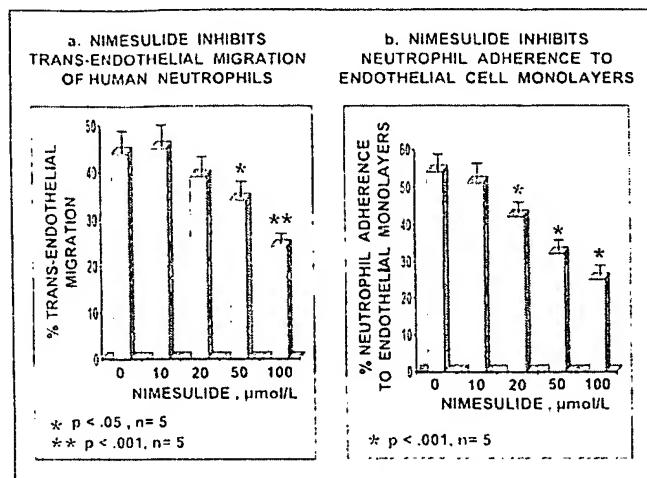


Fig. 6. Actions of nimesulide on neutrophil-endothelial cell interactions. Effects of nimesulide on the migration of neutrophils through endothelial cells (a) and on neutrophil adherence to endothelial cell monolayers (b).

a, b. Based on data from Dapino et al. (1994)

Confirmation of the actions *in vivo* in humans of nimesulide on neutrophil oxidative reactions has been provided by Ottonello and co-workers (1992) who showed that oral ingestion of 100 mg nimesulide lowered the phagocytic superoxide generation of neutrophils in response to opsonized zymosan particles and *N*-formylmethionyl-leucyl-phenylalanine (Fig. 5).

In contrast to the effects on neutrophils, nimesulide (>0.1 $\mu\text{mol/L}$) reduces the survival of human monocytes suggesting that this drug may have selective actions on apoptosis or other actions that affect growth of monocytes (Sawada et al., 2000).

An important action of nimesulide not observed with many other NSAIDs is its ability to inhibit the release of histamine from mast cells (Casolario et al., 1993; de Paulis et al., 1997; Kolaczkowska et al., 2002). This effect probably has significance not only in vasodilatation in acute inflammation but also for the wide range of actions of histamine now known to be of importance in chondrocytes and other cells involved in joint manifestations of arthritic diseases (Tanaka et al., 1997).

In addition to effects on mast cells, nimesulide inhibits chemotaxis and production of reactive oxygen species (ROS) and leukotriene C₄ production by eosinophils (Tool et al., 1996); these effects may be of significance in control by the drug in airways inflammation and allergic reactions although proof of the clinical effects is not yet available.

It has been postulated that a central or basic action of nimesulide in elevating intracellular levels of the key cell signal, cyclic 3',5'-AMP (cAMP) may account for the wide-ranging inhibitory effects on inflammatory cells and release of cartilage degrading enzymes (e.g. matrix metalloproteinases) (Barrachini et al., 1998; Kullick et al., 2002; Bevilacqua et al., 2004). Figure 7 shows the central role that elevation of cAMP plays in mediating these actions. Confirmation of the effect of nimesulide on cAMP in PMNs has been shown in which the activity of the enzyme that degrades cAMP, phosphodiesterase IV, is inhibited at concentrations

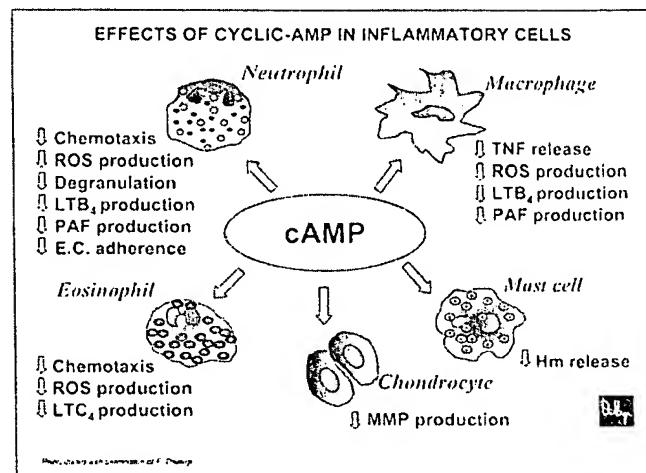


Fig. 7. The central actions on leucocytes, mast cells and chondrocytes of nimesulide as a consequence of regulation of cyclic-3',5'-adenosine monophosphate (cAMP). It is postulated that as nimesulide increases production of cAMP as a consequence of inhibition of phosphodiesterase-IV; this increased cAMP leads to reduced production of a wide range of inflammatory mediators by neutrophils, macrophages, mast cells and eosinophils. The reduction via cAMP in the cytokine stimulated release as well and the direct effects on the activity of metalloproteinases (MMP) especially of stromelysin (MMP-3), MMP-1 and MMP-8 from chondrocytes (Barrachini et al., 1998; Kullick et al., 2002; Bevilacqua et al., 2004; Manicourt et al., 2005) may, with the actions of nimesulide in activating glucocorticoid receptors, may contribute to reduced degradation of cartilage in osteoarthritis.

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$\geq 1 \mu\text{mol/L}$ coincident with increase in intracellular cAMP. This increase causes activation of protein kinase A which leads to inhibition of the various functional responses shown in Figure 7.

The potential protective effects of nimesulide on cartilage-degradation may be due to inhibition of the activity and production of metalloproteinases (Barrachini et al., 1998; Kullick et al., 2002; Bevilacqua et al., 2004; Manicourt et al., 2005), urokinase (Pelletier et al., 1997), expression of pro-inflammatory cytokines (Pelletier et al., 1997; Fahni et al., 2001), increased production of plasminogen activator inhibitor-1 (Pelletier et al., 1997) as well as the induction and activity of COX-2 (Di Battista et al., 2001; Fahni et al., 2001). Nimesulide reverses the inhibitory effects of interleukin-1 on cartilage proteoglycan synthesis, as well as inhibiting interleukin-1 induced production of oxyradicals by cartilage and nitric oxide by chondrocytes (Rainsford et al., 2002). Overall, the results from these various biochemical studies suggest that nimesulide might have a role in the protection of cartilage degradation in arthritic disease (Barrachini et al., 1998; Kullick et al., 2002; Bevilacqua et al., 2004; Manicourt et al., 2005), in contrast with other NSAIDs some of which may accelerate this degradation process (Rainsford et al., 1992; Walker and Rainsford, 1997). The therapeutic significance of these observations can be seen in clinical studies in which therapeutic doses of nimesulide, but not ibuprofen, showed to significantly decrease the serum levels of MMP's (Fig. 8), including stromelysin (or matrix metalloprotease-3, MMP-3) (Kullick et al., 2002; Kalajdzic et al., 2002; Bevilacqua et al., 2004), which may be related to

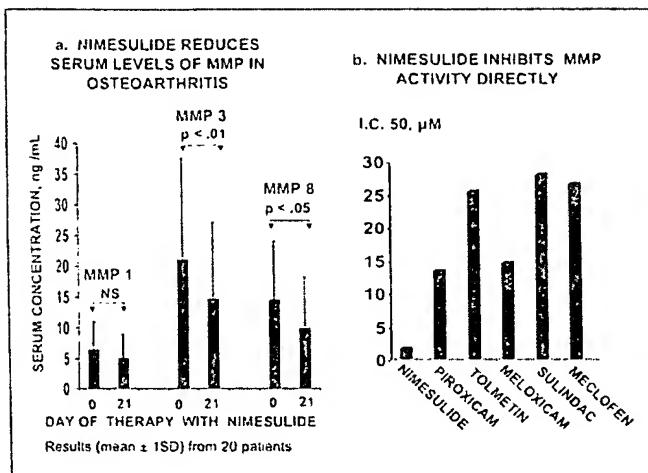


Fig. 8. Actions of nimesulide in reducing levels of metallo-proteinases (MMP's) in the serum of patients with osteoarthritis that had taken nimesulide [a], and of MMP enzymatic activity *in vitro* [b].

a. Based on data from Kullck et al. (2002)

b. Based on data from Barracchini et al. (1998)

reduction in the serum levels of hyaluronan (Bevilacqua et al., 2004), and the C-terminal cross-linking telopeptide of collagen II (Kalajdzic et al., 2002) both biomarkers which predicts a poor outcome of the osteoarthritis joint disease.

A recent observation by the Pelletier group concerning the effect of nimesulide in activating the glucocorticoid receptor and so producing inhibition of the transcription of COX-2 (DiBattista et al., 2001; Fahmi et al., 2001), so inhibiting the translation of the mRNAs for MMP's and pro-inflammatory cytokines (Pelletier et al., 1999). This may represent a novel and far-reaching action of the drug not seen with other NSAIDs. Further studies are, however, needed to confirm the effects of nimesulide on glucocorticoid receptor activation coincident with reduction in expression of the mRNA for proteins regulating production of the abovementioned inflammatory mediators.

In conclusion, nimesulide has a range of multi-factorial actions *in vitro*, some of which have been demonstrated *ex vivo* or *in vivo* in patients (Bennett and Villa, 2000; Bennett, 2001); these effects are summarised in Figure 9. Many of these are most likely related to core effects in causing inhibition of the production and actions of COX-2, cyclic AMP and glucocorticoid receptors, which appear to underlie the anti-inflammatory activity of nimesulide. The preferential inhibitory effects on COX-2, *ex vivo* inhibition of phagocytosis (as an effect related to ROS) and levels of serum MMP-3 and MMP-8 are actions of the drug that have been shown in humans. In models of inflammation in rats, nimesulide has been found to reduce PGE₂, TNF_α and neutrophil accumulation in inflammatory exudates thus providing further support for the multi-factorial actions *in vivo*. These multiple actions of the drug mean that the expression of anti-inflammatory activity is a consequence of regulation of the production and actions of a wide range of mediators of inflammation in contrast to the sole dependence of effects on production of prostaglandins from COX-2 activity as observed with NSAIDs such as the coxibs.

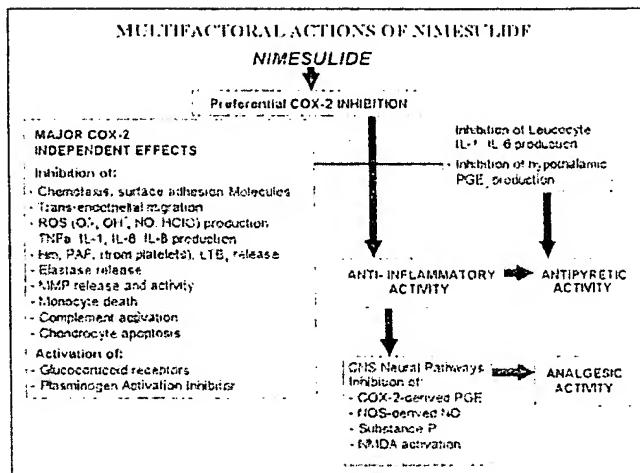


Fig. 9. Summary of the multi-factorial actions of nimesulide involving prostaglandin-related, and non-prostaglandin-related effects.

Abbreviations: COX-2, cyclo-oxygenase-2, TNF_α, tumour necrosis factor- α , Hm, histamine, PAF, platelet activating factor, ROS, reactive oxygen species, MMP, metalloproteinase(s)

Analgesic Activity

The analgesic activity of nimesulide is partly due to the capability of reducing the activity of the CNS nociceptive system with an onset of action consistent with the pharmacokinetic characteristics of the drug (Rainsford et al., 2005). The well-established increase in prostaglandins in the central nervous system (CNS) during pain transmission is due to induction and activity of COX-2 (Yamamoto and Nozaki-Taguchi, 1996; Ohtori et al., 2004; Veiga et al., 2004; Hofacker et al., 2005), although there is some evidence that COX-1 may also be involved (Zhu et al., 2003). Furthermore, nitric oxide (NO) plays a significant role including mediating sensitisation in the transmission of pain in the CNS (Schulte et al., 2003; Schmidtke et al., 2003; Tassorelli et al., 2004). Its presence and sustained elevation is critical in maintaining central sensitisation whilst the inhibition of NOS as well as COX-2 reduces central sensitisation in pain models. Experimental studies in animal models have demonstrated that nimesulide inhibits COX-2 and nitric oxide synthases (NOS) in the spinal cord (Tassorelli et al., 2003) confirming the central action of the drug in humans (Sandrini et al., 2001, 2002).

Figure 10 shows the possible modes of action of nimesulide at the level of the dorsal horn which may represent a key region of the central nervous system affected by the drug. That central actions of nimesulide are important in control of spinal neurotransmission in humans is illustrated from the study shown in Figure 11 (Sandrini et al., 2001).

Some of the mechanisms of the analgesic actions of nimesulide that have been shown in experimental models require more extensive investigations in humans to establish the clinical significance of these actions. However, as nimesulide affects a considerable number of mediators involved in both peripheral and central nervous system mediation of pain relief in hyperalgesia (Rainsford et al., 2005).

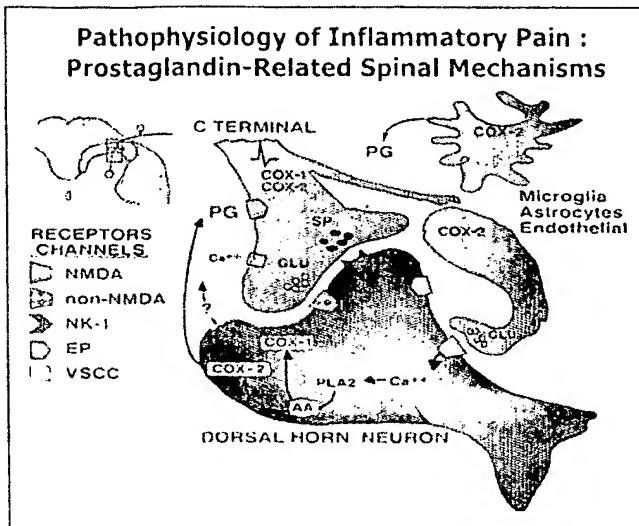


Fig. 10. Pathways involving prostaglandins (principally PGE₂) derived from cyclo-oxygenases 1 and 2 and their actions in mediating hyperalgesic responses to inflammatory pain in the dorsal horn. Induction of COX-2 during painful stimuli amplifies the production of PGE₂ and with this the stimulation of nerves impinging on and mediated from the dorsal horn via afferent nerves in the spinothalamic tracts of the central nervous system. PGE₂ production from activation of dorsal horn neurones by afferent inputs from C- and A_b-fibres causes (a) release of glutamate which acts on NMDA and non-NMDA receptors, and (b) release of substance P which acts on neurokinin-1 receptors (NK-1). The activation of these receptors leads to increased flux of Ca⁺⁺ ions that activate phospholipase-A₂ which in turn hydrolyzes phospholipids and release of arachidonic acid which serves as a substrate for COX-1 and COX-2. Nitric oxide synthase of the neuronal type, nNOS, is also activated and the nitric oxide produced during neural stimulation contributes to the activation of afferent pathways. Nimesulide inhibits release of PGE₂ and NO and so modulates neural transmission at the level of the dorsal horn. Whether sufficient concentration of the drug reach the dorsal horn to block COX-1 is not known. PGE₂ production from accessory cells (e.g. microglia, astrocytes) and endothelial cells also contributes to the cycle of activation of dorsal horn cells. From Bianchi et al. (2005); unpublished figure.

The fast onset of pain relief which is evident 15 min after oral intake of the drug is evident from studies in human volunteers where the spinal nociceptive transmission was determined after intake of nimesulide compared with placebo (Fig. 11) (Sandrini et al., 2001, 2002). These observations are paralleled in humans by the reduction of pain from ingestion of nimesulide which was apparent after 15 min from the administration, with a statistically significant superior onset of action being apparent versus the comparator drugs (Fig. 12) (Bianchi and Broggini, 2002).

In addition to affecting production of spinal PGE₂, nimesulide appears to influence the actions of NO in neural transmission (Sandrini et al., 2002). Undoubtedly, the rapid onset of analgesia by nimesulide is linked to the pharmacokinetic properties of the drug. Thus, after oral administration of 50 to 200 mg nimesulide tablets to healthy volunteers, plasma C_{max} values, ranging from 2.0 to 9.9 mg/L, are achieved quite rapidly within 1.7 to 3.2 h (Bernareggi, 1998). Studies in rheumatic patients have shown that relatively high nimesulide concentrations are present in inflamed synovial tissues and at earlier times than plasma

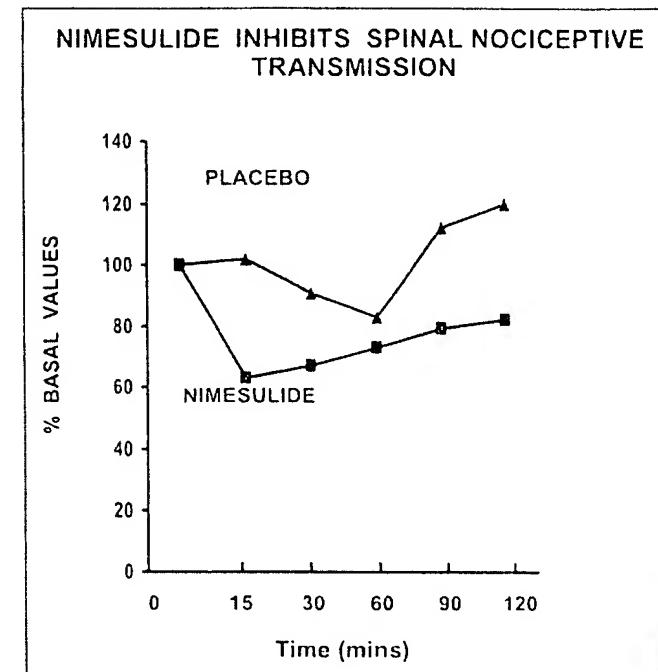


Fig. 11. Effects of nimesulide compared with placebo on spinal nociceptive transmission in human volunteers. From Sandrini et al. (2001).

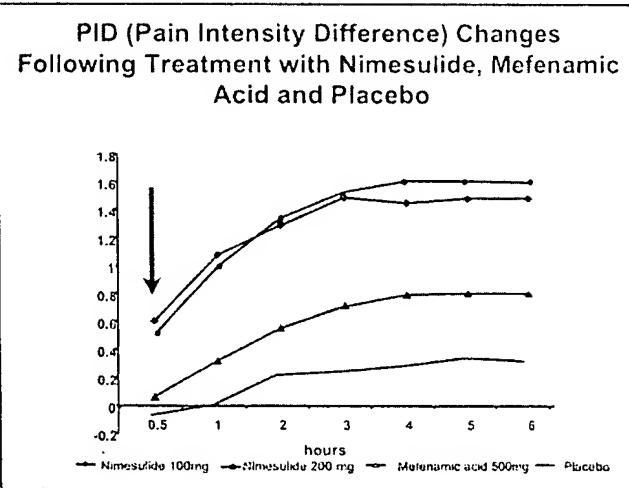


Fig. 12. Pain Intensity Difference (PID) Scores following dental surgery over a 6 h period following oral ingestion of 100 or 200 mg nimesulide compared with a comparable analgesic/anti-inflammatory dose of mefenamic acid and showing superior effects of both these NSAIDs over placebo. The dental surgery pain model is one of the frequently used human pain models which are very responsive to NSAIDs and analgesics. The effects of NSAIDs have been found to relate to inhibition of PGE₂, substance P and other mediators of acute inflammation. From Ragot et al. (1994).

peak times (Ligniere et al., 1990). The rapid accumulation in synovial fluids is also accompanied by rapid reduction in synovial fluid concentrations of PGE₂ (Duffy et al., 2003), thus indicating the synovial fluid pharmacodynamics of nimesulide coincides with the expression of pharmacological actions of the drug.

There is, however, evidence of reduced bio-equivalence of some copy and generic versions of nimesulide that can affect the pharmacokinetics of the drug compared with that of the original formulation of nimesulide (e.g. Aulin®) (Maroni and Gazzaniga, 2005). Any reduction in bioavailability of nimesulide would be expected to result in lower efficacy. A gel formulation of nimesulide has been found to have pharmacokinetic properties like that of diclofenac gel with comparable absorptive properties that favour local application to inflamed tissues and joints (Sengupta et al., 1998; Bianchi et al., 2005).

Clinical Applications

Over 200 clinical trials have been conducted in more than 90,000 patients with nimesulide in a variety of acute and chronic inflammatory and painful conditions (Ward and Brogden, 1988; Rabaseda, 1996; *Anonymous*, 1998; Bianchi et al., 2005).

1. Acute pain

The rapid onset of action of nimesulide is particularly evident in a variety of painful conditions where acute inflammation is the most predominant component. Thus, nimesulide has been shown to consistently reduce pain and where studied the inflammatory reactions and found to be superior to placebo and comparable or in some cases better than reference NSAIDs in (a) the treatment of soft tissue injuries and extra-articular trauma (where the gel formulation also gives good pain relief) (Ward and Brogden, 1988; Calligaris et al., 1993; Dreiser and Riebenfeld 1993a, 1993b; Lecomte et al., 1994; Jenoure et al., 1998; Dhaon et al., 1998, 2000), (b) various ear, nose and throat (ENT) inflammatory conditions (e.g. otitis, sore throat) (Milvio, 1984; Bianchini et al., 1993; Ottavani et al., 1993), (c) dental surgery (Cornaro, 1983; Ferrari Parabita et al., 1993; Pierleoni et al., 1993; Ragot et al., 1993, 1994; Scolari et al., 1999; Bracco et al., 2004), (d) odonto-stomatological pain (Salvato et al., 1984; Bucci et al., 1987; Moniaci et al., 1988) and (e) a range of post-operative conditions (Stefanoni et al., 1990; Ramella et al., 1993; Binning, 2004). In the dental pain model nimesulide demonstrates rapid onset of action and is more potent than comparable doses of mefenamic acid and placebo (Fig. 12) (Ragot et al., 1994). In this model it is of interest to note that the pain relief (measured as Pain Intensity Difference (PID) Scores were the same over the time interval up to 6hrs following 100 mg compared with 200 mg nimesulide, suggesting there the 100 mg dose is adequate (Pierleoni et al., 1993). These observations can be related to the non-linear plasma kinetics of the drug which deviates above 100 mg dosage (Bernareggi, 1998).

In all the studies involving investigation of acute pain nimesulide has been as effective as effective as the most widely used NSAIDs (e.g. naproxen, ibuprofen, diclofenac, mefenamic acid and celecoxib and rofecoxib) where it frequently showed superior or similar efficacy but with evidence of a better GI tolerability (Bianchi and Broggini, 2002, 2003).

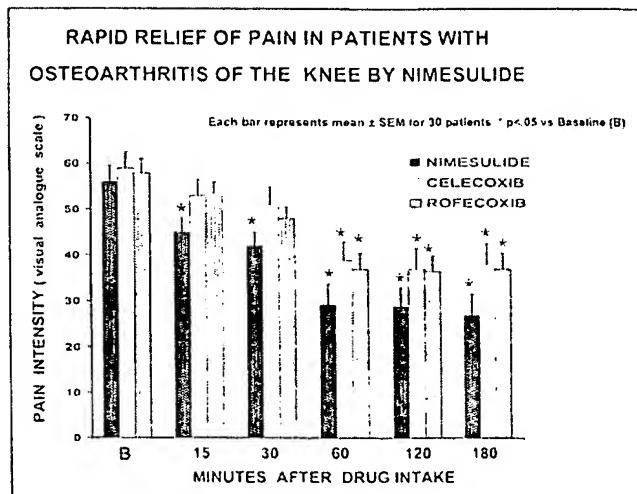


Fig. 13. Onset of pain relief in knee osteoarthritis from oral nimesulide compared with celecoxib and rofecoxib. From Bianchi and Broggini (2003).

2. Pain and Joint Inflammation in Osteoarthritis

NSAIDs are among the mostly widely-used drugs for the symptomatic treatment of painful osteoarthritis (Kean and Buchanan, 2005). The recommendations for therapy of pain and joint inflammation in this condition by the American College of Rheumatology. Subcommittee on Osteoarthritis Guidelines in 2000 (Kean and Buchanan, 2005) state that:

1. Paracetamol may give pain relief in mild osteoarthritis, but NSAIDs are more effective.
2. NSAIDs are superior to paracetamol in more severe osteoarthritis.
3. Paracetamol can be dangerous in patients with a history or current alcohol abuse or other liver injury.
4. Paracetamol can (in high doses) cause GI bleeds and ulcers.

Thus, NSAIDs are considered as a valid alternative to the first choice treatment, paracetamol, with particular reference to flares up when the first choice treatment may result inadequate. The critical point is to choose an NSAID with a low GI risk. This is where nimesulide has a place in therapy of osteoarthritis.

As noted earlier nimesulide has been found to have relatively rapid onset of analgesic action in hyperalgesia in humans when compared with well-established NSAIDs such as diclofenac and the two coxibs, celecoxib and rofecoxib (Bianchi and Broggini, 2002). In osteoarthritis, nimesulide also has a rapid onset of analgesia in comparison with the celecoxib and rofecoxib (Fig. 13) (Bianchi and Broggini, 2003).

In addition to producing rapid pain relief, the action of nimesulide in arthritic joints such as the inhibitory activity on COX-2 and NO activity, the prevention of cytokine-induced cartilage degradation compared with other NSAIDs, the oxyradical-scavenging activity, and inhibitory effects on apoptosis give a credible basis for the use of nimesulide in osteoarthritis (OA) and other musculoskeletal joint diseases and trauma states in relation to effects on joint functions (Rainsford et al., 2002, 2005; Bianchi et al., 2005). Aside from this

pharmacological rationale there is also a large amount of data on the clinical effectiveness of nimesulide have been obtained from studies in a variety of experimental designs, among them placebo-controlled and double blind studies and large-scale including post-marketing evaluations (Fossaluzza and Montagnani, 1989; Pochobradsky et al., 1991; Blardi et al., 1992; Dreiser and Riebenfeld 1993b; Estevez et al., 1993; Bourgeois et al., 1994; Lucke et al., 1994; Quattrini and Paladin, 1995; Porto et al., 1998; Roy et al., 1999; Sharma et al., 1999; Huskisson et al., 1999; Zgradic, 1999; Kriegel et al., 2001; Fioravanti et al., 2002; Bianchi and Broggini, 2003; Herrera and Gonzales, 2003; Omololu et al., 2005; Bianchi et al., 2005).

In these studies nimesulide significantly reduced the signs and symptoms of OA with an efficacy at least comparable to the reference drugs, including etodolac (Lucke et al., 1994), diclofenac (Estevez et al., 1993; Porto et al., 1998; Huskisson et al., 1999; Zgradic, 1999; Omololu et al., 2005), ketoprofen (Dreiser and Riebenfeld, 1993b), naproxen (Fossaluzza and Montagnani, 1989; Quattrini and Paladin, 1995; Kriegel et al., 2001; Fioravanti et al., 2002), piroxicam (Drieser and Riebenfeld, 1993b; Sharma et al., 1999) as well as the coxibs, celecoxib (Bianchi and Broggini, 2003) and rofecoxib (Bianchi and Broggini, 2003; Bourgeois et al., 1994)). Of particular importance is that several studies (Blardi et al., 1992; Bourgeois et al., 1994; Porto et al., 1998; Woher, 1999) have shown the relative safety of the drug, especially in relation to the gastrointestinal tract (Porto et al., 1998) and economic advantages (Liaropoulos, 1999; Tarricone et al., 2001) of nimesulide in the treatment of osteoarthritis as well as other musculo-skeletal conditions (Woher, 1999; Pohjolainen et al., 2000).

3. Primary Dysmenorrhoea

The use of NSAIDs in the treating primary dysmenorrhoea is particularly indicated as this painful condition is directly linked to modification in prostaglandin production and affects over 50% of all menstruating women (Ylikorkala and Dawood, 1978; Jamieson and Steege, 1996; Harlow and Park, 1996; Smith, 1997; Coco, 1999). NSAIDs are well established therapies for the relief of menstrual cramps and other symptoms of primary dysmenorrhoea (Coco, 1999; Dawood, 1988, 1993; Stones and Mountfield, 2000). In a number of studies nimesulide has been found to reduce pain and menstrual symptoms (Moggian et al., 1986; Pulkkinen, 1987, 2001; Lopez Rosales et al., 1989; Pulkkinen et al., 1992; Pirhonen et al., 1995; Melis et al., 1997; Facchinetto et al., 2001). Moreover, studies in more than 1400 women, over 1000 of which treated with nimesulide, widely document the activity of nimesulide in decreasing the intrauterine pressure, Doppler assessment of arterial blood flow and the reduction of PGF_{2α}; the latter plays a key role in the pain perception (Pulkkinen, 1987; Pulkkinen, et al., 1992; Pirhonen and Pulkkinen, 1995). Rapid onset of pain relief was observed with nimesulide in comparison with other NSAIDs, e.g. diclofenac (Facchinetto et al., 2001).

4. Headache, ENT Infections, Fever and Minor Pain States

Like other NSAIDs (Rainsford, 2004b) nimesulide has well documented evidence for relieving symptoms associated

with migrainous and non-migraine headaches, upper respiratory tract, ear nose and throat infections with associated fever, as well as in minor pain states (Reiner and Massers, 1984; Reiner et al., 1985; Antonelli et al., 1993; Cunietti et al., 1993; Giacovazzo et al., 1993; Zuckermann et al., 1993; Goyal et al., 1998; Neimark et al., 2004) (also reviewed in Bianchi et al., 2005). A particular advantage in the respiratory conditions is the relatively low likelihood of asthmatic and other allergic reactions with nimesulide (Bianco et al., 1993; Senna et al., 1996; Bianchi et al., 2005).

5. Cancer Pain

NSAIDs represent the first step in the World Health Organization guideless for stepwise analgesia in cancer pain (Rainsford, 2004b). Nimesulide has been shown to have analgesic activity in various cancer pain states, with activity that is comparable with that of established NSAIDs such as diclofenac and naproxen (Ventafredda et al., 1990; Galucci et al., 1992; Corli et al., 1993; Toscani et al., 1993). Of particular value is the use of the suppository formulation of nimesulide which as shown in a study by Corli et al. (1993) to have a rapid onset and sustained pain relief.

There is much interest in the potential for NSAIDs to prevent the development of cancer (Ulrich et al., 2006). Recent studies in experimental models suggest that nimesulide may have the potential for cancer chemoprevention in colorectal and lung cancers (Rainsford, 2005a), head and neck cancer (Lin et al., 2002) and from topical application in oral cancers (Sood et al., 2005). There are multiple actions of nimesulide on cancer cells including its inhibitory effects on COX-2 activity, signal transduction pathways, angiogenesis and selective activation of apoptosis that may be implicated in arresting cancer cell growth and prevention of the spread of tumours (Rainsford, 2005a). A recent report indicated that nimesulide nimesulide has inhibitory effects on oestrogen metabolism by aromatase activity in breast cancer cells which may have significance for prevention of breast cancer (Brueggemeier et al., 2005).

5. Conclusions

The extensive studies and over 20 years of successful clinical use of nimesulide in treating musculo-skeletal and acute and chronic pain states has shown the drug exhibits rapid and sustained control of inflammation and pain.

Adverse Reactions and Relative Safety

Several reviews have been published in recent years on the adverse reaction profile of nimesulide in comparison with that of other NSAIDs (Rainsford, 1996, 1998, 1999b, 2001; Bianco et al., 1993; Senna et al., 1996; Conforti et al., 2001; Lanas 2001; Boelsterli, 2002a, 2000b; Traversa et al., 2003; Laporte et al., 2004). These studies show that nimesulide has, overall, a pattern of organ reactions similar to that from other NSAIDs, though there are quantitative differences in the incidence of adverse reactions.

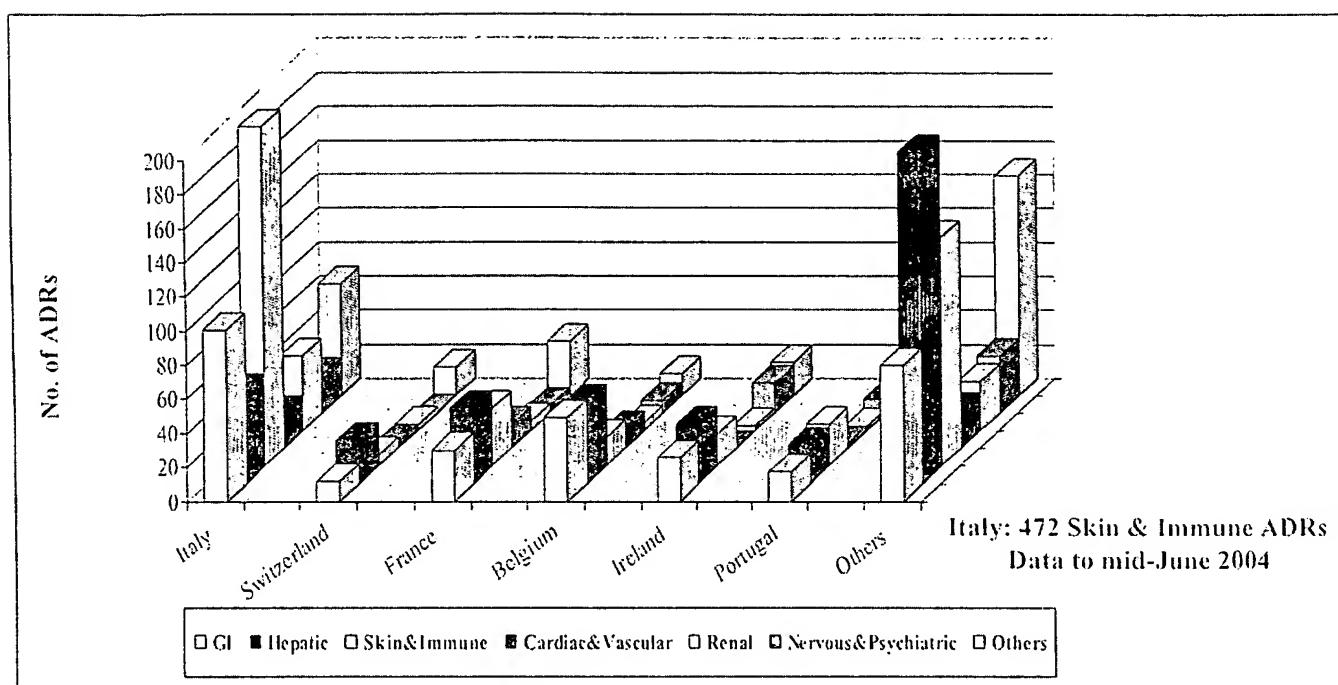


Fig. 14. Adverse Drug Reactions (ADRs), both serious and non-serious, from nimesulide by body system reported in the main countries where this drug has been marketed. From Bjarnason et al. (2005).

A comprehensive review was recently undertaken by Bjarnason and co-workers (2005) of all aspects of the relative safety and the mechanisms that are understood to underlie the adverse reactions from nimesulide. The data reviewed was derived from (a) epidemiological studies, (b) spontaneous reports of adverse drug reactions (ADRs) reported to Helsinn Healthcare SA, the WHO Nimbus Database and in published reports, (c) controlled clinical investigations in human volunteers and patients, (d) studies in laboratory animal models *in vivo* involving conventional toxicological and bioassays or pharmacological investigations designed to establish mode of action in relation to known adverse events (e.g. gastric acid secretion, parameters of renal function), and (e) *in vitro* studies in cellular or tissue systems, molecular biological and biochemical and molecular studies investigating mechanisms of toxic reactions or physiological functions in target organs wherein adverse events are known to occur. Detailed review of these investigations is found in Bjarnason et al. (2005) to which the reader is referred. Here the principal observations of the adverse reactions and toxic effects in the major organ systems are summarized thus:

(1) Overall pattern of adverse reactions

Figure 14 shows the overall pattern of serious adverse reactions in the main countries where nimesulide has been marketed by Helsinn Healthcare SA since the introduction of the drug in 1985. The majority of reactions have been in the skin and immune systems with fewer being evident in the GI, hepatic and renal systems; this is at variance with the pattern observed with classical NSAIDs, where ADRs

in the GI system usually predominate (Rainsford and Velo 1984, 1985; Rainsford, 1996, 1998, 1999a, 2001; McGettigan et al., 2000; Lanas, 2001; Laporte et al., 2004).

(2) Gastrointestinal tract:

Serious GI events from nimesulide are rare; in the past 5 years these have averaged 1.1 cases per 10^6 treatment courses (Bjarnason et al., 2005). Serious GI ADRs comprise 15.7% of all reports of which 4.4% were fatal but possibly not due to the drug. Pharmaco-epidemiological studies in case-control, cohort or hospitalization studies have given risk assessments (Relative Risk or Odds Ratios) of 1.2, 2.0 and 4.0 respectively with reference drugs excepting ibuprofen (for which the values are comparable) exceeding these by 2–5 fold.

Gastro-duodenal endoscopy and intestinal permeability studies have shown that nimesulide 100 mg b.i.d. produces little if any GI damage (Bjarnason and Thjodleifson, 1999). This contrasts with naproxen 500 mg b.i.d. or other conventional NSAIDs, which all produce visual evidence of gastroduodenal damage and with the former increased intestinal permeability and inflammation. As noted earlier in the section on pharmacological studies these low GI effects of nimesulide can be related to sparing of gastric mucosal and plasma COX-1 combined with its properties of controlling histamine release from mast cells, apparent anti-acid secretory activity, inhibitory effects on leucocyte emigration and activation, antioxidant activity and possibly effects on the production and actions of proinflammatory cytokines. Data from studies in experimental animal models strongly

supports the epidemiological data showing that nimesulide has a relatively low risk of serious GI reactions especially in comparison with other NSAIDs.

(2) Hepatic

Hepato-biliary disorders associated with nimesulide account for 14.3% of all serious ADRs, while abnormal laboratory findings comprise 6.6% of these, principally abnormal liver function tests. Like other NSAIDs, nimesulide is infrequently associated with elevation of the liver transaminases (ALT, AST, γ-GT), and less so with liver function tests (ALP, free and conjugated bilirubin) and, rarely, cholestatic jaundice. In most cases cessation of the drug results in restoration to normal of elevated liver transaminases and liver function tests (Bjarnason et al., 2005).

In pharmaco-epidemiological studies (Traversa et al., 2003) the occurrence of hepatopathy from nimesulide is at the upper end of the range compared with NSAIDs. The relative risks are in the range of 1.3–1.4. Most cases have confounding factors (other hepatotoxic drugs or liver diseases) (Rainsford, 1998, 1999b; Boelsterli et al., 2002a, 2002b). High concentrations (up to 100 μmol/L) of nimesulide, its metabolites and manufacturing impurities have not been found to cause direct cytotoxic damage to liver cells in culture (Rainsford et al., 2001), although increased cell damage is evident when paracetamol or other hepatotoxic drugs are present (K D Rainsford, unpublished studies). Thus it is unlikely that the drug or its metabolites have direct actions on liver cells. It is possible that the liver reactions attributed to nimesulide are idiosyncratic (Boelsterli, 2002b). Considerable evidence exists to show that most liver ADRs have been in patients that have taken hepatotoxic drugs and/or have liver diseases.

The formation of nitroso or hydroxylamine reactive metabolites of nimesulide has been suggested to be responsible for the liver damage from the drug (Boelsterli, 2002b), like that of reactive metabolite injury from diclofenac, paracetamol and other hepatotoxins (Boelsterli, 2002a). There is no evidence to support this reactive metabolite hypothesis of cell injury by nimesulide. Reduction in mitochondrial ATP and other functions has been observed with nimesulide following administration of high doses of the drug to rats. This phenomenon is related to uncoupling of oxidative phosphorylation like that observed with acidic NSAIDs and might account for the development of liver injury by these drugs. Reduction in ATP may initiate apoptosis by these drugs.

(3) Renal

Renal and urinary tract disorders comprise 4.7 % of all ADRs reported and are rare. These resemble those encountered with other NSAIDs (Bjarnason et al., 2005). They include tubular and interstitial nephritis, nephritic syndrome and renal failure.

Inhibition of renal prostaglandin production accounts for the transient physio-pathological renal effects of the drug on electrolyte balance, water impairment, and renin production; these being similar to those of other NSAIDs. Renal

ADRs that appear in the elderly are related to impaired renal clearance of the drug.

(4) Cutaneous and allergic reactions

Nimesulide is frequently associated with minor skin reactions (erythematous rashes, urticaria etc); these being akin to those with other NSAIDs (Rainsford, 1992). Stevens-Johnson and Lyell's syndromes have been rarely reported; the occurrence of these reactions may be lower than observed with other NSAIDs. Intolerance to nimesulide is rare in patients with pseudo-allergic reactions to other NSAID and aspirin-sensitive asthmatic patients (Bianco et al., 1993; Senna et al., 1996).

(5) Cardiovascular system

Serious cardiovascular reactions (myocardial infarction, congestive heart failure) are rare with nimesulide (EMEA 2005a, 2005b) and do not appear as frequent as observed with coxibs. (US Food and Drug Administration, Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Committee, 2005a; US Food and Drug Administration EDA Public Health Advisory, 2005b). Mild blood pressure changes have been observed with nimesulide (Rainsford, 1999) and this is also observed with most NSAIDs and could be related to COX-2 inhibition (Khanna et al., 2005; Topol, 2004; US Food and Drug Administration, Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Committee, 2005a; US Food and Drug Administration FDA Public Health Advisory, 2005b).

(6) Role of Pharmacokinetics

The role of pharmacokinetics of nimesulide in determining adverse reactions and toxicity has been reviewed (Rainsford, 1999b; Bernareggi and Rainsford, 2005). The likelihood of drug accumulation upon repeated dosage (i.e. after steady state levels of the drug have been achieved at 7 days) in elderly patients without hepato-renal conditions is rare. As shown in Figure 18 the clearance and volume of distribution of nimesulide is unaffected by age. Furthermore, there are no differences in pharmacokinetic parameters between the sexes (Fig. 19) (Bernareggi and Rainsford, 2005) such as observed with some NSAIDs (e.g. the salicylates (Rainsford, 1996, 2004)). Of the drug interactions those affecting pharmacokinetics include the reduction by nimesulide in the bioavailability of furosemide when taken with nimesulide concomitant with reduction in the natriuretic and, to a lesser extent, the kaliuretic effects of this drug (Bernareggi and Rainsford, 2005). The pharmacokinetics of warfarin, digoxin (in patients with mild congestive heart disease), theophylline and glybencamide are mostly unaffected by nimesulide and vice versa (Bernareggi and Rainsford, 2005). Prothrombin times during treatment with warfarin or acenocoumarol are unaffected by nimesulide (Rainsford, 1999b). Reduced plasma levels of theophylline have, however, been found in

patients with chronic obstructive lung disease that received nimesulide (Rainsford, 1999b). Cimetidine and antacids do not affect the bioavailability of nimesulide (Bernareggi and Rainsford, 2005) possibly because the ionisation of the drug in the stomach is not an issue for its absorption. Some drugs affect the protein binding of nimesulide but probably these are not sufficient to be of clinical significance. These observations suggest that there are few significant drug interactions between nimesulide and other drugs that may be taken by patients with osteoarthritis or other musculo-skeletal conditions.

Benefit/risk profile

Based on what has been discussed above the following conclusions can be drawn on the overall benefit/risk profile of nimesulide.

The therapeutic benefits of nimesulide have been compared with both placebo and the most widely used NSAIDs for the main approved indications, including acute pain, treatment of painful osteoarthritis and primary dysmenorrhoea. Nimesulide proved to be a valid alternative to other NSAIDs, with a similar or even superior clinical efficacy characterized by a fast onset of action.

As evident in the safety section, nimesulide shares the characteristic side effects of NSAIDs, such as GI, skin, renal, hepatic reactions. Like other drugs in the class, the occurrence of adverse reactions suggesting hypersensitivity comprises a significant proportion of the total reactions. Analysis of the incidence of all adverse reactions from the available data confirms this to be in line with the class. In particular it can be affirmed that the incidence of upper GI perforation, bleeding and ulceration is low and that nimesulide is probably less prone to produce gastrointestinal bleeding than other NSAIDs. Incidence rate is similarly low for renal, serious skin and hepatic reactions.

Data on post marketing surveillance confirms that there is not signal of any changes in the clinical characteristics of listed serious and non-serious adverse reactions overtime or of any potentially 'new' adverse reactions or new signals related to nimesulide. This, together with the evidence from clinical studies, allows confirming that the favourable and invariant benefit risk profile of nimesulide.

References

American College of Rheumatology Subcommittee on Osteoarthritis Guidelines (2000): Recommendations for the medical management of osteoarthritis of the hip and knee. *Arthritis Rheum.*, **43**, 1905–15.

Anonymous (1998). In: Focus Nimesulide. (Aulin) Helsinn Healthcare SA. Adis International Ltd., Milan.

Antonelli, A., Cimino, A., Cimino, A., Di Girolamo, A., Filippi, P., Filippin, S. et al. (1993). [The treatment of ENT phlogosis: seuprose S vs. nimesulide]. *Acta Otorhinolaryngol Ital.*, **13 Suppl 39**, 1–16.

Bannwarth, B., Netter, P., Pourel, J., Royer, R. J., Gaucher, A. (1989). Clinical pharmacokinetics of nonsteroidal anti-inflammatory drugs in the cerebrospinal fluid. *Biomed Pharmacother.*, **43**, 121–6.

Barraacchini, A., Franceschini, N., Amicosante, G., Oratore, A., Minisola, G., Pantaleoni, G. et al. (1998). Can non-steroidal anti-inflammatory drugs act as metalloproteinase modulators? An in vitro study of the inhibition of collagenase activity. *J Pharm Pharmacol.*, **50**, 1417–23.

Bennett, A. (2001). Nimesulide: a well-established cyclooxygenase-2 inhibitor with many other pharmacological properties relevant to inflammatory diseases. In: Therapeutic Role of Selective COX-2 Inhibitors. Eds: Vane, J. R., Botting, R. M. London: William Harvey Press, 521–40.

Bennett, A., Villa, G. (2000). Nimesulide: an NSAID that preferentially inhibits COX-2, and has various unique pharmacological actions. *Exp Opin Pharmacother.*, **1**, 277–86.

Bernareggi, A. (1998). Clinical pharmacokinetics of nimesulide. *Clin Pharmacokinet.*, **35**, 247–74.

Bernareggi, A., Rainsford, K. D. (2005) Pharmacokinetics of nimesulide. In: Nimesulide. Actions and Uses. Ed. Rainsford, K. D. Basel: Birkhäuser, 63–120.

Bevilacqua, M., Devogelaer, J.-P., Righini, V., Famaey, J.-P., Manicourt, D.-H. (2004). Effect of nimesulide on the serum levels of hyaluronan and stromelysin-1 in patients with osteoarthritis: a pilot study. *Int J Clin Pract.*, **144** (Suppl), 13–9.

Bevilacqua, M., Vago, T., Baldi, G., Renesto, E., Dallegri, F., Norbiato, G. (1994). Nimesulide decreases superoxide production by inhibiting phosphodiesterase type IV. *Eur J Pharmacol.*, **268**, 415–23.

Bianchi, M., Ehrlich, G. E., Facchinetto, F., Huskisson, E. C., Jenoure, P., La Marca, A. et al. (2005). Clinical applications of nimesulide in pain, arthritic conditions and fever. In: Nimesulide. Actions and Uses. Ed. Rainsford, K. D. Basel: Birkhäuser, 245–313.

Bianchi, M., Broggini, M. (2002). Anti-hyperalgesic effects of nimesulide. Studies in rats and humans. *Int J Clin Pract.*, **128**, 11–9.

Bianchi, M., Broggini, M. (2003). A randomized, double blind, clinical trial comparing the efficacy of nimesulide, celecoxib and rofecoxib in osteoarthritis of the knee. *Drugs.*, **63** (Suppl 1), 37–46.

Bianchini, G., Scarieabarozzi, I., Montecorbo, U., Ceccarelli, A., Chiesa, F., Ditri, L. et al. (1993). Double-blind study of nimesulide in divers with inflammatory disorders of the ear, nose and throat. *Drugs.*, **46** (Suppl 1), 100–2.

Bianco, S., Robuschi, M., Petrigli, G., Seuri, M., Pieroni, M., Refini, R. M. et al. (1993). Efficacy and tolerability of nimesulide in asthmatic patients intolerant to aspirin. *Drugs.*, **46**, 115–20.

Bijlsma, J. W. (2002). Analgesia and the patient with osteoarthritis. *Am J Ther.*, **9**, 189–97.

Binning, A. R. (2004). Nimesulide in the treatment of acute pain: double-blind comparative study in a post-operative setting. 3rd World Congress of Pain, 21–25 September 2004, Barcelona. Abstracts of the Satellite Symposium on Nimesulide, The Control of Pain for a Better Compliance of the Patients.

Bjarnason, I., Bissoli, F., Conforti, A., Maiden, L., Moore, N., Moretti, U. et al. (2005). Adverse reactions and their mechanisms from nimesulide. In: Nimesulide. Actions and Uses. Ed: Rainsford, K. D. Basel: Birkhäuser, 315–415.

Bjarnason, I., Rainsford, K. D. (2001a). Are cyclooxygenase 2 inhibitors free of gastrointestinal side effects? *West J Med.*, **175**, 267–8.

Bjarnason, I., Rainsford, K. D. (2001b). COX-2 inhibitors and the gastrointestinal tract. *Gut*, **48**, 451.

Bjarnason, I., Thjodleifsson, B. (1999). Gastrointestinal toxicity of non-steroidal anti-inflammatory drugs: the effect of nimesulide compared with naproxen on the human gastrointestinal tract. *Rheumatology*, **38 Suppl 1**, 24–32.

Blardi, P., Gatti, F., Auteri, A., Di Perri, T. (1992). Effectiveness and tolerability of nimesulide in the treatment of osteoarthritic elderly patients. *Int J Tiss Res.*, **14**, 263–8.

Boelsterli, U. A. (2002a). Mechanisms of NSAID-induced hepatotoxicity. *Drug Safety*, **25**, 633–48.

Boelsterli, U. A. (2002b). Nimesulide and hepatic adverse effects: roles of reactive metabolites and host factors. *Int J Clin Pract* (Suppl 28), 30–6.

Bourgeois, P., Dreiser, R. L., Lequesne, M. G., Macciocchi, A., Monti, T. (1994). Multi-centre double-blind study to define the most favourable dose of nimesulide in terms of efficacy/safety ratio in the treatment of osteoarthritis. *Eur J Rheum Inflamm.*, **14**, 39–50.

Bourgeois, P., Dreiser, R. L., Lequesne, M. G., Macciochetti, A., Monti, T. (1994). Multi-centre double-blind study to define the most favourable dose of nimesulide in terms of efficacy/safety ratio in the treatment of osteoarthritis. *Eur J Rheumatol Inflamm.* 14, 39–50.

Bracco, P., Debernardi, C., Cosecia, D., Pasqualini, D., Pasqualicchio, F., Calabrese, N. (2004). Efficacy of rofecoxib and nimesulide in controlling postextraction pain in oral surgery: a randomised comparative study. *Curr Med Res Opin.* 20, 107–12.

Bravo-Cuellar, A., Garcia-Reyes, G., Barba-Barajas, M., Carranco-Lopez, A., Dominguez-Rodriguez, J. R., Orbach-Arbouys, S. (2003). Modification by nimesulide administration of the phagocytic activity of polymorphonuclears of healthy subjects. *Biomed Pharmacother.* 57, 434.

Brogden, R. N. (1986). Non-steroidal anti-inflammatory analgesics other than salicylates. *Drugs.* 32 Suppl 4, 27–45.

Brueggemann, R. W., Diaz-Cruz, E. S., Li, P. K., Sugimoto, Y., Lin, Y. C., Shapiro, C. L. (2005). Translational studies on aromatase, cyclooxygenases, and enzyme inhibitors in breast cancer. *J Steroid Biochem Mol Biol.* 95, 129–36.

Brune, K., Graf, P., Rainford, K. D. (1977). A pharmacokinetic approach to the understanding of therapeutic effects and side effects of salicylates. *Agents and Actions.* Suppl 1, 9–26.

Bucci, E., Mignogna, M. D., Bucci, P. (1987). Aulin: a new modern treatment for inflammatory disorders in dentistry. *Min Stomatol.* 36, 101–3.

Calligaris, A., Scaricabarozzi, I., Vecchiet, L. (1993). A multicentre double-blind investigation comparing nimesulide and naproxen in the treatment of minor sport injuries. *Drugs.* 46 (Suppl 1), 187–90.

Casolari, V., Meliota, S., Marino, O., Patella, V., de Paulis, A., Guidi, G., Marone, G. (1993). Nimesulide, a sulfonanilide nonsteroidal anti-inflammatory drug, inhibits mediator release from human basophils and mast cells. *J Pharmacol Exp Ther.* 267, 1375–85.

Cappechi, P. L., Ceccatelli, L., Beermann, U., Laghi Pasini, F., Di Perri, T. (1993). Inhibition of neutrophil function in vitro by nimesulide. Preliminary evidence of an adenosine-mediated mechanism. *Arzneim Forsch.* 43, 992–6.

Celotti, F., Laufer, S. (2001). Anti-inflammatory drugs: new multitarget compounds to face an old problem. The dual inhibition concept. *Pharmacol Res.* 43, 429–36.

Coco, A. S. (1999). Primary dysmenorrhea. *Am Fam Physician.* 60, 489–96.

Conforti, A., Leone, R., Moretti, U., Mozzo, F., Velo, G. (2001). Adverse drug reactions related to the use of NSAIDs with a focus on nimesulide. *Drug Safety.* 24, 1081–90.

Corli, O., Cozzolino, A., Scaricabarozzi, I. (1993). Nimesulide and diclofenac in the control of cancer-related pain. Comparison between oral and rectal administration. *Drugs.* 46, 152–5.

Cornaro, G. (1983). A new non-steroidal anti-inflammatory drug in the treatment of inflammations due to parodontal surgery. *Curr Ther Res.* 33, 982–9.

Cunicitti, E., Monti, M., Vigano, A., Aprile, E. D., Saligari, A., Scafuro, E. et al. (1993). Nimesulide in the treatment of hyperpyrexia in the aged. *Drug Research.* 2, 160–2.

Dallegrì, F., Ottomello, L., Bevilacqua, M. (1995). Possible modes of action of nimesulide in controlling neutrophilic inflammation. *Arzneim Forsch.* 45, 1114–7.

Dallegrì, F., Ottomello, L., Dapino, P., Bevilacqua, M. (1992a). The anti-inflammatory drug nimesulide rescues alpha-1-proteinase inhibitor from oxidative inactivation by phagocytosing neutrophils. *Respiration.* 59, 1–4.

Dallegrì, F., Ottomello, L., Dapino, P., Sacchetti, C. (1992b). Effect of nonsteroidal anti-inflammatory drugs on the neutrophil promoted inactivation of alpha-1-proteinase inhibitor. *J Rheumatol.* 19, 419–23.

Dallegrì, F., Patroni, F., Ballesterro, A., Ottomello, L., Ferrando, F., Sacchetti, C. (1990). Inactivation of neutrophil-derived hypochlorous acid by nimesulide: a potential mechanism for the tissue protection during inflammation. *Int J Tissue React.* 12, 107–11.

Dapino, P., Ottomello, L., Dallegrì, F. (1994). The anti-inflammatory drug nimesulide inhibits neutrophil adherence to and migration across monolayers of cytokine-activated endothelial cells. *Respiration.* 61, 336–41.

Davis, R., Brogden, R. N. (1994). Nimesulide. An update of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs.* 48, 431–54.

Dawood, M. Y. (1988). Nonsteroidal anti-inflammatory drugs and changing attitudes toward dysmenorrhoea. *Am J Med.* 8, 23–9.

Dawood, M. Y. (1993). Nonsteroidal antiinflammatory drugs and reproduction. *Am J Obstet Gynecol.* 169, 1255–65.

Day, R. O. (2001). Pharmacokinetic and pharmacodynamic aspects of the ideal COX-2 inhibitor: a rheumatologist's perspective. *Clin Exp Rheumatol.* 19 (Suppl 25), S59–62.

de Laval, X., Delarge, J., Somers, E., de Tullio, P., Henrotin, Y., Pirotte, B. et al. (2000). Recent advances in inducible cyclooxygenase (COX-2) inhibition. *Curr Med Chem.* 7, 1041–62.

de Paulis, A., Ciccarelli, A., Marino, I., de Crescenzo, G., Marino, D., Marone, G. (1997). Human synovial mast cells. II. Heterogeneity of the pharmacologic effects of antiinflammatory and immunosuppressive drugs. *Arthritis Rheum.* 40, 469–78.

Dhaon, B. K., Farooque, M. F., Sharma, D. R., Bhutani, S. (1998). Open labelled clinical evaluation of local application of nimesulide transdermal gel in painful musculoskeletal conditions. *Indian J Orthop.* 32, 75–8.

Dhaon, B. K., Singh, O. P., Gupta, S. P., Maini, L., Sharma, D. R., Bhutani, S. (2000). Efficacy and safety of nimesulide transdermal gel versus diclofenac and piroxicam gel in patients with acute musculoskeletal condition. *Indian J Orthop.* 34, 288–92.

Di Battista, J. A., Fahmi, H., He, Y., Zhang, M., Martel-Pelletier, J., Pelletier, J. P. (2001). Differential regulation of interleukin-1 beta-induced cyclooxygenase-2 gene expression by nimesulide in human synovial fibroblasts. *Clin Exp Rheumatol.* 19 (1 Suppl 22), S3–5.

Dreiser, R. L., Riebenfeld, D. (1993a). A double-blind study of the efficacy of nimesulide in the treatment of ankle sprain in comparison with placebo. *Drugs.* 46 (Suppl 1), 183–6.

Dreiser, R. L., Riebenfeld, D. (1993b). Nimesulide in the treatment of osteoarthritis. Double-blind studies in comparison with piroxicam, ketoprofen and placebo. *Drugs.* 46 (Suppl 1), 191–5.

Duffy, T., Belton, O., Bresnihan, B., FitzGerald, O., FitzGerald, D. (2003). Inhibition of PGE₂ production by nimesulide compared with diclofenac in the acutely inflamed joint of patients with arthritis. *Drugs.* 63 (Suppl 1), 31–6.

Estevez, F., Amoro, G., Giusti, M., Lasalvia, L., Havranek, H. (1993). Diclofenac vs nimesulida en artrosis. Niveles plasmaticos y eficacia clinica. *Medicina (Buenos Aires)* 53, 307–14.

European Medicines Agency (2005a). European Medicines Agency concludes action on COX-2 inhibitors. Press Release, London, 27 June 2005: www.emea.eu.int.

European Medicines Agency (2005b). European Medicines Agency update on non-selective NSAIDs. Press Release, London, 17 October, 2005: www.emea.eu.int.

Evans, A. M. (1996). Pharmacodynamics and pharmacokinetics of the profens: enantioselectivity, Clinical implications, and special reference to S(+)-ibuprofen. *J Clin Pharmacol.* 36 (Suppl), 7S–15S.

Facchinetto, F., Picciolini, F., Sgarbi, L., Renzetti, D., Volpe, A. (2001). Nimesulide in the treatment of primary dysmenorrhoea: a double-blind study versus diclofenac. *Drugs of Today.* 37, 39–45.

Fahmi, H., He, Y., Zhang, M., Martel-Pelletier, J., Pelletier, J. P., Di Battista, J. A. (2001). Nimesulide reduces interleukin-1 beta-induced cyclooxygenase-2 gene expression in human synovial fibroblasts. *Osteoarthritis Cartilage.* 9, 332–40.

Famaey, J. P. (1997) Review. In vitro and in vivo pharmacological evidence of selective cyclooxygenase-2 inhibition by nimesulide: An overview. *Inflamm Res.* 46, 437–46.

Feldman, M., McMahon, A. T. (2000). Do cyclooxygenase-2 inhibitors provide benefits similar to those of traditional nonsteroidal anti-inflammatory drugs, with less gastrointestinal toxicity? *Ann Intern Med.* 132, 134–43.

Ferrari Parabita, G., Zanetti, U., Scalvini, E., Rossi, D., Scaricabarozzi, I. (1993). A controlled clinical study of the efficacy and tolerability of nimesulide vs naproxen in maxillo-facial surgery. *Drugs.* 46 (Suppl 1), 171–3.

Ferreira, S. H., Moncada, S., Vane, J. R. (1971). Indomethacin and aspirin abolish prostaglandin release from the spleen. *Nat New Biol.*, **231**, 237–9.

Fioravanti, A., Storri, L., DiMartino, S., Bisogno, S., Oldani, V., Scotti, A., et al. (2002). A randomised, double-blind, multicenter trial of nimesulide-beta-cyclodextrin versus naproxen in patients with osteoarthritis. *Clin Ther.*, **24**, 504–19.

Flower, R., Gryglewski, R., Herbaezynska-Cedro, K., Vane, J. R. (1972). Effects of anti-inflammatory drugs on prostaglandin biosynthesis. *Nat New Biol.*, **238**, 104–6.

Fossaluzza, V., Montagnani, G. (1989). Efficacy and tolerability of nimesulide in elderly patients with osteoarthritis: double-blind trial versus naproxen. *J Int Med Res.*, **17**, 295–303.

Gallucci, M., Toscani, F., Mapelli, A., Cantarelli, A., Veca, G., Scaricabarozzi, L. (1992). Nimesulide in the treatment of advanced cancer pain. Double-blind comparison with naproxen. *Arzneim Forsch.*, **42**, 1028–30.

Giacovazzo, M., Gallo, M. F., Guidi, V., Rico, R., Scaricabarozzi, L. (1993). Nimesulide in the treatment of menstrual migraine. *Drugs*, **46** Suppl 1, 140–1.

Gomez-Gaviro, M. V., Gonzalez-Alvaro, I., Dominguez-Jimenez, C., Peschon, J., Black, R. A., Sanchez-Madrid, F., et al. (2002). Structure-function relationship and role of tumor necrosis factor-alpha-converting enzyme in the down-regulation of L-selectin by non-steroidal anti-inflammatory drugs. *J Biol Chem.*, **277**, 38212–21.

Goyal, P. K., Chandra, J., Unnikrishnan, G., Kumari, S., Passah, S. M. (1998). Double blind randomized comparative evaluation of nimesulide and paracetamol as antipyretics. *Indian Pediatr.*, **35**, 519–22.

Graf, P., Glatt, M., Brune, K. (1975). Acidic nonsteroid anti-inflammatory drugs accumulating in inflamed tissue. *Experientia*, **31**, 951–3.

Harlow, S. D., Park, M. (1996). A longitudinal study of risk factors for the occurrence, duration and severity of menstrual cramps in a cohort of college women. *Br J Ob Gyn.*, **103**, 1134–8.

Hart, F. D., Huskisson, E. C. (1984). Non-steroidal anti-inflammatory drugs: Current status and rational therapeutic use. *Drugs*, **27**, 232–55.

Hayball, P. J. (1996). Chirality and nonsteroidal anti-inflammatory drugs. *Drugs*, **52** Suppl 5, 47–58.

Herrera, J. A., Gonzalez, M. (2003). Comparative evaluation of the effectiveness and tolerability of nimesulide versus rofecoxib taken once a day in the treatment of patients with knee osteoarthritis. *Am J Ther.*, **10**, 468–72.

Heyneman, C. A., Lawless-Liday, C., Wall, G. C. (2000). Oral versus topical NSAIDs in rheumatic diseases: a comparison. *Drugs*, **60**, 555–74.

Hofacker, A., Coste, O., Nguyen, H. V., Marian, C., Scholich, K., Geisslinger, G. (2005). Downregulation of cytosolic prostaglandin E₂ synthase results in decreased nociceptive behavior in rats. *J Neurosci.*, **25**, 9005–9.

Hotz-Behofsits, C. M., Walley, M. J. M., Simpson, R., Bjarnason, I. T. (2003). COX-1, COX-2 and the topical effect in NSAID-induced enteropathy. *Inflammopharmacology*, **10**, 363–70.

Hunneyball, I. M., Billingham, M. E. J., Rainsford, K. D. (1989). Animal Models of Arthritic Disease: Influence of Novel Compared with Classical Anti-Rheumatic Agents. In: *New Developments in Anti-Rheumatic Therapy*. Eds: K. D. Rainsford and G. P. Velo. Lancaster: Kluwer Academic Publishers, 93–131.

Huntjens, D. R., Danhof, M., Della Pasqua, O. E. (2005). Pharmacokinetic-pharmacodynamic correlations and biomarkers in the development of COX-2 inhibitors. *Rheumatology*, **44**, 846–59.

Huskisson, E. C., Macciochi, A., Rahlf, V. W., Bernstein, R. M., Breinher, A. D., Doyle, D. V., et al. (1999). Nimesulide versus diclofenac in the treatment of osteoarthritis of the hip or knee: an active control equivalence study. *Curr Ther Res.*, **60**, 253–65.

Jamieson, D. J., Steege, J. F. (1996). The prevalence of dysmenorrhoea, dyspareunia, pelvic pain, and irritable bowel syndrome in primary care practices. *Obstet Gynecol.*, **87**, 55–8.

Jenoune, P., Gorshevsky, O., Ryf, C., Steigbügel-Werzel, C., Frey, W., Voisin, D. (1998). Randomised, double-blind, multicentre study of nimesulide vs diclofenac in adults with other sport injuries. *J Clin Res.*, **1**, 343–56.

Jüni, P., Rutjes, A. W. S., Dieppe, P. A. (2002). Are selective COX 2 inhibitors superior to traditional non steroid anti-inflammatory drugs? *Br Med J.*, **324**, 1287–8.

Kalajdzic, T., Faour, W. H., He, Q. W., Fahmi, H., Martel-Pelletier, J., Pelletier, J. P., et al. (2002). Nimesulide, a preferential cyclooxygenase 2 inhibitor, suppresses peroxisome proliferator-activated receptor induction of cyclooxygenase 2 gene expression in human synovial fibroblasts: evidence for receptor antagonism. *Arthritis Rheum.*, **46**, 494–506.

Kean, W. F., Buchanan, W. W. (2005). The use of NSAIDs in rheumatic disorders 2005: a global perspective. *Inflammopharmacology*, **13**, 343–70.

Khanna, D., Khanna, P. P., Furst, D. E. (2005). COX-2 controversy: where do we go from here? *Inflammopharmacology*, **13**, 395–402.

Kimura, T., Iwase, M., Kondo, G., Watanabe, H., Ohashi, M., Ito, D., et al. (2003). Suppressive effect of selective cyclooxygenase-2 inhibitor on cytokine release in human neutrophils. *Int Immunopharmacol.*, **3**, 1519–28.

Kitchen, E. A., Dawson, W., Rainsford, K. D., Cawston, T. (1985). Inflammation and possible modes of action of anti-inflammatory drugs. In: *Anti-Inflammatory and Anti-Rheumatic Drugs. Volume I: Inflammation and Mechanisms and Actions of Traditional Drugs*. Ed. Rainsford, K. D. CRC Press: Boca Raton (FL), 21–87.

Kolaczkowska, E., Shahzidi, S., Seljelid, R., van Rooijen, N., Plytycz, B. (2002). Early vascular permeability in murine experimental peritonitis is co-mediated by resident peritoneal macrophages and mast cells: crucial involvement of macrophage-derived cysteinyl-leukotrienes. *Inflammation*, **26**, 61–71.

Kriegel, W., Korff, K. J., Ehrlich, J. C., Lehnhardt, K., Macciochi, A., Moresino, C., et al. (2001). Double-blind study comparing the long-term efficacy of the COX-2 inhibitor nimesulide and naproxen in patients with osteoarthritis. *Int J Clin Pract.*, **55**, 510–4.

Kullick, W. C., Niksic, E., Klein, G. (2002). Effect of nimesulide on metallo-proteinase and matrix degradation in osteoarthritis: A pilot clinical study. *Int J Clin Pract.*, **128** (Suppl), 24–9.

Lanas, A. (2001). Cyclo-oxygenase-1/cyclo-oxygenase-2 non-selective non-steroidal anti-inflammatory drugs: epidemiology of gastrointestinal events. *Dig Liver Dis.*, **33** Suppl 2, S29–34.

Landoni, M. F., Soraci, A. (2001). Pharmacology of chiral compounds: 2-arylpropionic acid derivatives. *Curr Drug Metab.*, **2**, 37–51.

Laporte, J. R., Ibanez, I., Vidal, X., Vendrell, I., Leone, R. (2004). Upper gastro-intestinal bleeding associated with the use of NSAIDs: newer vs. older agents. *Drug Safety*, **27**, 411–20.

Lecomte, J., Buyse, H., Taymans, J., Monti, T. (1994). Treatment of tendinitis and bursitis: a comparison of nimesulide and naproxen sodium in a double-blind parallel trial. *Eur J Rheumatol Inflamm.*, **14**, 29–32.

Leiskowith, J. B. (1999). Cyclooxygenase-2 specificity and its clinical implications. *Am J Med.*, **106**(5B), 43S–50S.

Levy, R. A., Smith, D. L. (1989). Clinical differences among nonsteroidal anti-inflammatory drugs: implications for therapeutic substitution in ambulatory patients. *Drug Intell Clin Pharm.*, **23**, 76–85.

Liaropoulos, L. (1999). Economic comparisons of nimesulide and diclofenac and the incidence of adverse events in the treatment of rheumatic disease in Greece. *Rheumatology*, **38** (Suppl 1), 39–46.

Lignière, G. C., Tamborini, U., Panarace, G. (1990). La nimesulide nel liquido sinoviale do paziente con artrite reumatoide. *Farmacia Terapia*, **7**, 173–6.

Lin, D. T., Subbaramaiah, K., Shah, J. P., Dannenberg, A. J., Boyle, J. O. (2002). Cyclooxygenase-2: a novel molecular target for the prevention and treatment of head and neck cancer. *Head Neck*, **24**, 792–9.

Lopez-Rosales, C., Cisneros-Lugo, J. H., Romo-Esciso, L. J., Garcia-Sandoval, M. G. (1989). [Nimesulide in the treatment of primary dysmenorrhea. Comparative clinical evaluation with mefenamic acid and fentiazac]. *Cinecol Obstet Mex.*, **57**, 196–201.

Lucker, P. W., Pawlowski, C., Friederich, I. (1994). Double-blind randomized multicentre clinical study evaluating the efficacy and tolerability of nimesulide in comparison with etodolac in patients

suffering from osteoarthritis of the knee. *Eur J Rheum Inflamm.* 14, 29–38.

Manicourt, D. H., Bevilacqua, M., Righini, V., Famaey, J. P., Devogelaer, J. P. (2005). Comparative effect of nimesulide and ibuprofen on the urinary levels of collagen type II C-telopeptide degradation products and on the serum levels of hyaluronan and matrix metalloproteinases-3 and -13 in patients with flare-up of osteoarthritis. *Drugs R D* 6, 261–71.

Maroni, A., Gazzaniga, A. (2005). Pharmaceutical formulations of nimesulide. In: Nimesulide. Actions and Uses. Ed. Rainsford K D. Basel, Birkhäuser. 121–32.

McGettigan, P., Platonov, A., Henry, D. A. (2000). Renal and cardiovascular toxicity of non-steroidal anti-inflammatory drugs. *Inflammopharmacology*, 8, 1–18.

Melis, G. B., Paolelli, A. M., Muis, V., Ajossa, S., Guerriero, S. (1997). Studio clinico controllato sull'efficacia e tollerabilità del metoxibutropato verso nimesulide in campo ginecologico. *Minerva Ginecol.* 49, 409–15.

Milvio, C. (1984). Nimesulide for the treatment of painful inflammatory process in the ear, nose and throat areas: a double-blind controlled study with benzydamine. *J Int Med Res.* 12, 327–32.

Moggiani, G., Pellegrini, E., Tamburini, E., Pini, P., Tumidei, U. (1986). [A new pharmacologic treatment of primary dysmenorrhea]. *Clin Ter.* 117, 481–92.

Monaci, D., Mozzati, M., Anglesio Fariua, G., Giacomelli, E. (1998). Valutazione della-eticaccia e della tollerabilità della nimesulide in alcune patologie odontostomatologiche. *Stomatologica*, 37, 291.

Mouithys-Mickalad, A. M., Zheng, S. X., Deby-Dupont, G. P., Deby, C. M., Lamy, M. M., Reginster, J. Y. et al. (2000). In vitro study of the antioxidant properties of non steroid anti-inflammatory drugs by chemiluminescence and electron spin resonance (ESR). *Free Radic Res.* 33, 607–21.

Nakatani, K., Takeshita, S., Tsujimoto, H., Kawamura, Y., Sekine, I. (2001). Inhibitory effect of serine protease inhibitors on neutrophil-mediated endothelial cell injury. *J Leukoc Biol.* 69, 241–7.

Neimark, A. I., Iakovets, I. V., Aliev, R. T. (2004). [Naiz (nimesulid) in combined treatment of patients with chronic non-bacterial prostatitis with chronic pelvic pain syndrome]. *Urologija*, 5, 31–4. [Russian]

Netter, P., Bannwarth, B., Lapicque, F., Demotes-Mainard, F., Scheeverbeke, T., Gillet, P. (1993). Pharmacokinetics and pharmacodynamics of non steroid anti-inflammatory drugs in synovial fluid. *Agents Actions Suppl* 44, 45–50.

Ohtori, S., Takahashi, K., Aoki, Y., Doya, H., Ozawa, T., Saito, T. et al. (2004). Spinal neural cyclooxygenase-2 mediates pain caused in a rat model of lumbar disk herniation. *J Pain*, 5, 385–91.

Omololu, B., Alonge, T. O., Ogundade, S. O., Aduroja, O. O. (2005). Double blind clinical trial comparing the safety and efficacy of nimesulide (100mg) and diclofenac in osteoarthritis of the hip and knee joints. *West Afr J Med.* 24, 128–33.

Oster, A. J. K., Hazleman, B. L. (2005). The murky waters of the coxibs: a review of the current state of play. *Inflammopharmacology*, 13, 371–81.

Ottaviani, A., Mantovani, M., Scaricabarozzi, I. (1993). A multicentre clinical study of nimesulide in inflammatory diseases of the ear, nose and throat. *Drugs*, 46 (Suppl 1), 96–9.

Ottomello, L., Amelotti, M., Barbera, P., Dapino, P., Mancini, M., Tortolino, G. et al. (1999). Chemoattractant-induced release of elastase by tumor necrosis factor-primed human neutrophils: auto-regulation by endogenous adenosine. *Inflamm Res.* 48, 637–42.

Ottomello, L., Dapino, P., Pastorino, G., Dallegrli, F. (1992). Inhibition of the neutrophil oxidative response induced by the oral administration of nimesulide in normal volunteers. *J Clin Lab Immunol.* 37, 91–6.

Ottomello, L., Dapino, P., Pastorino, G., Montagnani, G., Gatti, F., Guidi, G. et al. (1993). Nimesulide as a downregulator of the activity of the neutrophil myeloperoxidase pathway. Focus on the histoprotective potential of the drug during inflammatory processes. *Drugs*, 46 Suppl 1, 29–33.

Ottomello, L., Dapino, P., Scirocco, M. C., Balbi, A., Bevilacqua, M., Dallegrli, F. (1995). Sulphonamides as anti-inflammatory agents: old drugs for new therapeutic strategies in neutrophilic inflammation? *Clin Sci.* 88, 331–6.

Pehourcq, F., Matoga, M., Bannwarth, B. (2004). Diffusion of arylpropionate non-steroidal anti-inflammatory drugs into the cerebrospinal fluid: a quantitative structure-activity relationship approach. *Fundam Clin Pharmacol.* 18, 65–70.

Pelleter, J. P., Di Battista, J. A., Zhang, M., Fernandes, J., Alaeddine, N., Martel-Pelleter, J. (1999). Effect of nimesulide on glucocorticoid receptor activity in human synovial fibroblasts. *Rheumatology*, 38 (Suppl 1), 11–3.

Pelleter, J. P., Mineau, F., Fernandes, J., Kiansa, K., Ranger, P., Martel-Pelleter, J. (1997). Two NSAIDs, nimesulide and naproxen, can reduce the synthesis of urokinase and IL-6 while increasing PAI-1, in human OA synovial fibroblasts. *Clin Exp Rheumatol.* 15, 393–8.

Pierleoni, P., Tonelli, P., Scaricabarozzi, I. (1993). A double-blind comparison of nimesulide and ketoprofen in dental surgery. *Drugs*, 46 (Suppl 1), 168–70.

Pirhonen, J., Pulkkinen, M. (1995). The effect of nimesulide and naproxen on the uterine and ovarian arterial blood flow velocity. A Doppler study. *Acta Obstet Gynecol Scand.* 74, 549–53.

Pochobradsky, M. G., Mele, G., Beretta, A., Montagnani, G. (1991). Post-marketing surveillance of nimesulide in the short-term treatment of osteoarthritis. *Drugs Expt Clin Res.* 17, 197–204.

Pohjolainen, T., Jekunen, A., Autio, L., Vuorela, H. (2000). Treatment of acute low back pain (LBP) with the COX-2 selective NSAR nimesulide: Results of a randomised, double-blind, comparative trial vs. ibuprofen. *Spine*, 25, 1579–85.

Porto, A., Reis, C., Perdigoto, R., Leone, R., Goncalves, M., Freitas, P. et al. (1998). Gastrointestinal tolerability of nimesulide and diclofenac in patients with osteoarthritis. *Curr Ther Res.* 59, 654–65.

Pulkkinen, M., Monti, T., Maciocchi, A. (1992). Analysis of uterine contractility after administration of the non-steroidal anti-inflammatory drug nimesulide. *Acta Obstet Gynecol Scand.* 71, 181–5.

Pulkkinen, M. O. (1987). Alterations in intrauterine pressure, menstrual fluid prostaglandin F levels, and pain in dysmenorrhoeic women treated with nimesulide. *J Clin Pharmacol.* 27, 65–9.

Pulkkinen, M. O. (2001). Is there a rationale for the use of nimesulide in the treatment of dysmenorrhoea? *Drugs of Today*, 37, 31–8.

Quattrini, M., Paladin, S. (1995). A double blind study comparing nimesulide and naproxen in the treatment of osteoarthritis of the hip. *Clin Drug Invest.* 10, 139–46.

Rabasseda, X. (1996). Nimesulide: a selective cyclooxygenase 2 inhibitor anti-inflammatory drug. *Drugs of Today*, 32, 365–84.

Ragot, J.-P., Giorgi, M., Marinoni, M., Macchi, M., Mazza, P., Rizzo, S. et al. (1994). Acute activity of nimesulide in the treatment of pain after oral surgery-double-blind, placebo and mefenamic acid controlled study. *Europ J Clin Res.* 5, 39–50.

Ragot, J. P., Monti, T., Maciocchi, A. (1993). Controlled clinical investigation of acute analgesic activity of nimesulide in pain after oral surgery. *Drugs*, 46 (Suppl. 1), 162–7.

Rainsford, K. D. (1975). A synergistic interaction between aspirin, or other non-steroidal anti-inflammatory drugs, and stress which produces severe gastric mucosal damage in rats and pigs. *Agents and Actions*, 5, 553–8.

Rainsford, K. D. (1977). Towards assays of gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with improved predictive value in man. *Agents and Actions*, 7, 245–8.

Rainsford, K. D. (1992). Mechanism of rash formation and related skin conditions induced by non-steroidal anti-inflammatory drugs. In: KD Rainsford, GP Velo (Eds): Side effects of Anti-inflammatory Drugs-3. Lancaster: Kluwer Academic Publishers. 287–301.

Rainsford, K. D. (1996). Mode of action, uses, and side effects of anti-inflammatory drugs. In: Advances in Anti-Rheumatic Therapy. Ed: Rainsford KD. Boca Raton (FL): CRC Press. 59–111.

Rainsford, K. D. (1998). An analysis from clinico-epidemiological data of the principal adverse events from the Cox-2 selective NSAID, nimesulide, with particular reference to hepatic injury. *Inflammopharmacology*, 6, 203–21.

Rainsford, K. D. (1999a). Profile and mechanisms of gastro-intestinal and other side-effects from NSAIDs. *Am J Med.* 107 (6A), 27S–36S.

Rainsford, K. D. (1999b). Relationship of nimesulide safety to its pharmacokinetics: Assessment of adverse reactions. *Rheumatology*, **38** (Suppl 1), 4–10.

Rainsford, K. D. (2001). The Ever-Emerging Anti-inflammatories. Have there been Any Real Advances? *J Physiol (Paris)*, **95**, 11–9.

Rainsford, K. D. (2004a). Inhibitors of eicosanoids. In: *The Eicosanoids*. Ed. P. Curtis Prior. Chichester: John Wiley. 189–210.

Rainsford, K. D. (2004b). Salicylates in the treatment of acute pain. In: Rainsford KD (ed). *Aspirin and Related Drugs*, CRC Press, Boca Raton (Florida). 587–618.

Rainsford, K. D. (2004c). Pharmacology and biochemistry of salicylates and related drugs. In: *Aspirin and Related Drugs*. Ed. K. D. Rainsford. Boca Raton (FL): CRC Press, 215–366.

Rainsford, K. D. (2005a). The discovery, development and novel actions of nimesulide. In: *Nimesulide. Actions and Uses*, Rainsford K. D. (Ed.). Basel: Birkhäuser, 1–61.

Rainsford, K. D. [Ed.] (2005b). *Nimesulide. Actions and Uses*. Basel: Birkhäuser.

Rainsford, K. D. (2005c). Introduction – the coxib controversies. *Inflammopharmacology*, **13**, 331–41.

Rainsford, K. D. [Ed.] (1997). *Side Effects of Anti-inflammatory Drugs IV*. Dordrecht: Kluwer Academic Publishers.

Rainsford, K. D., Bevilacqua, M., Dallegrì, F., Gago, F., Ottonello, L., Sandrini, G. et al. (2005). Pharmacological properties of nimesulide. In: *Nimesulide. Actions and Uses*. Ed. Rainsford K. D. Basel: Birkhäuser Verlag, 133–244.

Rainsford, K. D., Brune, K. (1978). Selective Cytotoxic Actions of Aspirin on Parietal Cells. A principal factor in the early stages of aspirin-induced gastric damage. *Archiv Toxicol*, **40**, 143–50.

Rainsford, K. D., Fox, S. A., Osborne, D. J. (1984). Comparative effects of some non-steroidal anti-inflammatory drugs on the ultrastructural integrity and prostaglandin levels in the rat gastric mucosa: Relationship to drug uptake. *Scand J Gastroenterol*, **19** (Suppl. 101), 55–68.

Rainsford, K. D., Fox, S. A., Osborne, D. J. (1985). Relationship between drug absorption, inhibition of cyclooxygenase and lipoxygenase pathways and the development of gastric mucosal damage by non-steroidal anti-inflammatory drugs in rats and pigs. In: *Advances in Prostaglandins, Leukotrienes and Lipoxins*, Ed. M. J. Bailey, New York: Plenum Press, 639–53.

Rainsford, K. D., Omar, H., Ashraf, A., Hewson, A. T., Bunning, R. A. D., Kishiraj, R. et al. (2002). Recent pharmacodynamic and pharmacokinetic findings on oxaprozin. *Inflammopharmacology*, **10**, 185–239.

Rainsford, K. D., Rashad, S. Y., Revell, P. A., Low, F. M., Hemingway, A. P., Walker, F. S. et al. (1992). Effects of NSAIDs on cartilage proteoglycan and synovial prostaglandin metabolism in relation to progression of joint deterioration in osteoarthritis. In: *Rheumatology. State of the Art Eds.* Bälint, G., Gömöri, B., Hadinka, L. Amsterdam: Elsevier, 177–83.

Rainsford, K. D., Schweitzer, A., Brune, K. (1981). Autoradiographic and biochemical observations on the distribution of non-steroidal anti-inflammatory drugs. *Arch Int Pharmacodyn*, **250**, 180–94.

Rainsford, K. D., Seabrook, R. W., Spencer, S., Hewson, A. T. (2001). Effects of nimesulide and metabolites or manufacturing intermediates on the viability and growth of the human hepatoma HepG2 cell line. *Life Sci*, **69**, 2965–73.

Rainsford, K. D., Velo, G. P. [Eds.] (1984). *Side-Effects of Anti-inflammatory/Analgesic Drugs*. New York: Raven Press.

Rainsford, K. D., Velo, G. P. [Eds.] (1985). *Side-Effects of Anti-Inflammatory Drugs. Part 1. Clinical and Epidemiological Aspects*. Lancaster: MTP Press, 1985.

Rainella, G., Costagli, V., Vetere, M., Capra, C., Casella, G., Sogni, A. et al. (1993). Comparison of nimesulide and diclofenac in the prevention and treatment of painful inflammatory postoperative complications of general surgery. *Drugs*, **46**, 159–61.

Redlak, M. J., Power, J. J., Miller, T. A. (2005). Role of mitochondria in aspirin-induced apoptosis in human gastric epithelial cells. *Am J Physiol Gastrointest Liver Physiol*, **289**, G731–8.

Reiner, M., Cereghetti, S., Haesemann, M., Monti, T. (1985). Antipyretic activity of nimesulide suppositories: double-blind versus diclofenac and placebo. *Int J Clin Pharmacol*, **23**, 673–7.

Reiner, M., Massers, E. (1984). Nimesulide in the treatment of fever: a double-blind crossover clinical trial. *J Int Med Res*, **12**, 102–4.

Rothstein, R. (1998). Safety profiles of leading nonsteroidal anti-inflammatory drugs. *Am J Med*, **105**(5A), 39S–43S.

Roy, V., Gupta, U., Sharma, S., Dhaon, B. K., Singh, N. P., Gulati, P. (1999). Comparative efficacy and tolerability of nimesulide and piroxicam in osteoarthritis with special reference to chondroprotection. *J Indian Med Assoc*, **97**, 442–5.

Salvato, A., Zambruno, E., Ventrini, E., Savio, G. (1984). Sperimentazione clinica di un nuovo antiedemigeno orale: nimesulide. *Giorn Stomat Orthognat*, **3**, 184–91.

Sánchez-Borges, M., Capriles-Hulett, A., Caballero-Fonseca, F. (2002). NSAID-induced urticaria and angioedema: a reappraisal of its clinical management. *Am J Clin Dermatol*, **3**, 599–607.

Sánchez-Borges, M., Capriles-Hulett, A., Caballero-Fonseca, F. (2003). Cutaneous reactions to aspirin and nonsteroidal antiinflammatory drugs. *Clin Rev Allergy Immunol*, **24**, 125–36.

Sandrini, G., Cecchini, P. A., Alfonso, E., Nappi, G. (2001). The effectiveness of nimesulide in pain. A neurophysiological study in humans. *Drugs of Today*, **37** (Suppl B), 21–9.

Sandrini, G., Tassorelli, C., Cecchini, A. P., Alfonso, E., Nappi, G. (2002). Effects of nimesulide on nitric oxide-induced hyperalgesia in humans – a neurophysiological study. *Eur J Pharmacol*, **450**, 259–62.

Schmidtko, A., Ruth, P., Geisslinger, G., Tegeder, I. (2003). Inhibition of cyclic guanosine 5'-monophosphate-dependent protein kinase I (PKG-I) in lumbar spinal cord reduces formalin-induced hyperalgesia and PKG upregulation. *Nitric Oxide*, **8**, 89–94.

Schoenfeld, P. (2001). An evidence-based approach to the gastrointestinal safety profile of COX-2 selective anti-inflammatories. *Gastroenterol Clinics Nth Amer*, **30**, 1027–44.

Schulte, G., Robertson, B., Fredholm, B. B., DeLander, G. E., Shortland, P., Molander, C. (2003). Distribution of antinociceptive adenosine A1 receptors in the spinal cord dorsal horn, and relationship to primary afferents and neuronal subpopulations. *Neuroscience*, **121**, 907–16.

Scolari, G., Lazzarin, F., Fornaseri, C., Carbone, V., Rengo, S., Amato, M. et al. (1999). A comparison of nimesulide beta cyclodextrin and nimesulide in postoperative dental pain. *Int J Clin Pract*, **53**, 345–8.

Sengupta, S., Velpandian, T., Kabir, S. R., Gupta, S. K. (1998). Analgesic efficacy and pharmacokinetics of topical nimesulide gel in healthy human volunteers: double-blind comparison with piroxicam, diclofenac and placebo. *Eur J Clin Pharmacol*, **54**, 541–7.

Senna, G. E., Passalacqua, G., Andri, G., Dama, A. R., Albano, M., Fregonese, L. et al. (1996). Nimesulide in the treatment of patients intolerant of aspirin and other NSAIDs. *Drug Safety*, **14**, 94–103.

Serhan, C. N. (2004). A search for endogenous mechanisms of anti-inflammation uncovers novel chemical mediators: missing links to resolution. *Histochem Cell Biol*, **122**, 305–21.

Shah, A. A., Thjodleifsson, B., Murray, F. E., Kay, E., Barry, M., Sigthorsson, G. et al. (2001). Selective inhibition of COX-2 in humans is associated with less gastrointestinal injury: a comparison of nimesulide and naproxen. *Gut*, **48**, 339–46.

Sharma, S., Rastogi, S., Gupta, V., Rohtagi, D., Gulati, P. (1999). Comparative efficacy and safety of nimesulide versus piroxicam in osteoarthritis with special reference to chondroprotection. *Am J Ther*, **6**, 191–7.

Shimizu, M., Tatsumi, M., Matsushita, R., Totsuka, J., Inoue, Y., Ohta, K. et al. (2003). Correlation between the physicochemical property of some nonsteroidal anti-inflammatory drugs and changes in adenosine triphosphate, glutathione and hemoglobin in rat erythrocytes. *Biol Pharm Bull*, **26**, 1155–65.

Sigthorsson, G., Thjodleifsson, B., Mahmud, T., Bjarnason, I. (2000a). Gastrointestinal tolerability of nimesulide, a selective cyclooxygenase-2 inhibitor, in experimental animals and man. *Inflammopharmacology*, **8**, 175–87.

Sigthorsson, G., Tibble, J., Mahmud, T., Bjarnason, I. (2000b). NSAID-induced gastrointestinal damage: the biochemical consequences of the ion trapping hypothesis. *Inflammopharmacology*, **8**, 31–41.

Simon, R. A., Namazy, J. (2003). Adverse reactions to aspirin and nonsteroidal antiinflammatory drugs (NSAIDs). *Clin Rev Allergy Immunol*, **24**, 239–52.

Smith, R. P. (1997). *Gynecology in primary care*. Baltimore: Williams and Wilkins. 389–404.

Sood S., Schiff S. J., Yang C. S., Chen X. (2005) Selection of topically applied non-steroidal anti-inflammatory drugs for oral cancer chemoprevention. *Oral Oncol*, 41, 562–7.

Stefanoni, G., Saccomanno, F., Scaricabarozzi, I., Volontieri, G., Persiani, L., Boselli, L. et al. (1990). Efficacia clinica della nimesulide in confronto a diclofenac sodio nella prevenzione e nel trattamento della sintomatologia algico-flogistica postchirurgica. *Minerva Chirurgica*, 45, 1469–75.

Stones, R. W., Mountfield, J. (2000). Interventions for treating chronic pelvic pain in women. Cochrane Database Syst Rev 2000; (2): CD000387. Update in: Cochrane Database Syst Rev 2000; (4): CD000387.

Swingle, K. F., Bell, R. L., Moore, G. G. I. (1985). Anti-inflammatory activity of antioxidants. In: *Anti-Inflammatory and Anti-Rheumatic Drugs. Volume III: Anti-Rheumatic Drugs, Experimental Agents, and Clinical Aspects of Drug Use*. Boca Raton (FL): CRC Press, 105–26.

Tanaka, K., Shimotori, T., Makino, S., Aikawa, Y., Inaba, T., Yoshida, C., Takano, S. (1992). Pharmacological studies of the new antiinflammatory agent 3-formylamino-7-methylsulfonylaminoo-6-phenoxy-4H-1-benzopyran-4-one. 1st communication: antiinflammatory, analgesic and other related properties. *Arzneimittelforschung*, 42, 935–44.

Tarnawski, A. S., Jones, M. K. (2003). Inhibition of angiogenesis by NSAIDs: molecular mechanisms and clinical implications. *J Mol Med*, 62, 27–36.

Tarricone, R., Martelli, E., Parazzini, F., Darba, J., Le Pen, C. (2001). Economic evaluation of nimesulide versus diclofenac in the treatment of osteoarthritis in France, Italy and Spain. *Clin Drug Invest*, 21, 453–64.

Tassorelli, C., Blandini, F., Greco, R., Nappi, G. (2004). Nitroglycerin enhances cGMP expression in specific neuronal and cerebrovascular structures of the rat brain. *J Chem Neuroanat*, 27, 23–32.

Tassorelli, C., Greco, R., Sandrini, G., Nappi, G. (2003). Central components of the analgesic/antihyperalgesic effect of nimesulide: studies in animal models of pain and hyperalgesia. *Drugs*, 63 (Suppl 1), 9–22.

Teoh, N. C., Farrell, G. C. (2003). Hepatotoxicity associated with non-steroidal anti-inflammatory drugs. *Clin Liver Dis*, 7, 401–13.

Tool, A. T., Mul, F. P., Knol, E. F., Verhoeven, A. J., Roos, D. (1996). The effect of salmeterol and nimesulide on chemotaxis and synthesis of PAF and LTC₄ by human eosinophils. *Eur Respir J*, 22 (Suppl), 141s–145s.

Tool, A. T., Verhoeven, A. J. (1995). Inhibition of the production of platelet activating factor and of leukotriene B₄ in activated neutrophils by nimesulide due to an elevation of intracellular cyclic adenosine monophosphate. *Arzneim Forsch*, 45, 1110–4.

Topol, E. J. (2004). Failing the public health – rofecoxib, Merck, and the FDA. *N Engl J Med*, 351, 1707–9.

Toscani, F., Gallucci, M., Scaricabarozzi, I. (1993). Nimesulide in the treatment of advanced cancer pain. Double-blind comparison with naproxen. *Drugs*, 46, 156–8.

Traversa, G., Bianchi, C., Da Cus, R., Abraha, I., Menniti-Ippolito, F., Venegoni, M. (2003). Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. *Br Med J*, 327, 18–22.

Uemura, S., Ochi, T., Sugano, K., Makuchi, R. W. (2003). Systematic review for evaluation of tolerability of nonsteroidal antiinflammatory drugs in osteoarthritis patients in Japan. *J Orthop Sci*, 8, 279–87.

Ulrich C. M., Bigler J., Potter J. D. (2006) Non-steroidal anti-inflammatory drugs for cancer prevention: promise, perils and pharmacogenomics. *Nature Rev Cancer*, 6, 130–140.

US Food and Drug Administration. Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Committee (2005a). Minutes of the joint meeting, February 16, 17 and 18, 2005. www.fda.gov/ohrms/dockets/ac/minutes/2005-4-90MI_final.doc 04-05-2005 (accessed 25/7/05).

US Food and Drug Administration. FDA Public Health Advisory (2005b). FDA announces important changes and additional warnings for COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). www.fda.gov/cder/drug/advisory/COX2.htm (accessed 25/7/05).

Vane, J. R. (1971). Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol*, 231, 232–5.

Vane, J. R., Botting, R. M. (1995) New insights into the mode of action of anti-inflammatory drugs. *Inflamm Res*, 44, 1–10.

Vane, J. R., Botting, R. M. [Eds] (2001). *Therapeutic Roles of Selective COX-2 Inhibitors*. London: William Harvey Press.

Veiga, A. P., Duarte, I. D., Avila, M. N., da Motta, P. G., Tatsuo, M. A., Francischetti, J. N. (2004). Prevention by celecoxib of secondary hyperalgesia induced by formalin in rats. *Life Sci*, 75, 2807–17.

Ventafredda, V., Toscani, F., Tamburini, M., Corli, O., Gallucci, M. (1990). Sodium naproxen vs. sodium diclofenac in cancer pain control. *Arzneim Forsch*, 40, 1132–8.

Verbeeck, R. K. (1990). Pharmacokinetic drug interactions with nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet*, 19, 44–66.

Verhoeven, A. J., Tool, A. T., Kuipers, T. W., Roos, D. (1993). Nimesulide inhibits platelet-activating factor synthesis in activated human neutrophils. *Drugs*, 46 Suppl 1, 52–8.

Walker, F. S., Rainsford, K. D. (1997) Do NSAIDs adversely affect joint pathology in osteoarthritis? In: *Side Effects of Anti-inflammatory Drugs – 4*. Ed. Rainsford, K. D. Lancaster: Kluwer Academic Publishers, 43–53.

Ward, A., Brogden, R. N. (1989). Nimesulide: a preliminary review of its pharmacological properties and therapeutic efficacy in inflammation or pain States. *Drugs*, 36, 732–53.

Warner, T. D., Giuliano, F., Vojnovic, I., Bukasa, A., Mitchell, J. A., Vane, J. R. (1999). Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci USA*, 96, 7563–8; erratum p 9666.

Wober, W. (1999). Comparative efficacy and safety of nimesulide and diclofenac in patients with acute shoulder and a meta-analysis of controlled studies with nimesulide. *Rheumatology*, 38, 33–8.

Yamamoto, T., Nozaki-Taguchi, N. (1996). Analysis of the effects of cyclooxygenase (COX)-1 and COX-2 in spinal nociceptive transmission using indometacin, a non-selective COX inhibitor, and NS-398, a COX-2 selective inhibitor. *Brain Res*, 739, 104–10.

Ylikorkala, O., Dawood, M. Y. (1978). New concepts in dysmenorrhoea. *Am J Obstet Gynecol*, 130, 833–5.

Yuan, Y., Hunt, R. H. (2003). Assessment of the safety of selective cyclooxygenase-2 inhibitors: where are we in 2003? *Inflammopharmacology*, 11, 337–54.

Zgradie, I. (1999). Comparison of therapeutic efficacy of nimesulide and diclofenac in patients with degenerative joint diseases. *J Indian Med Assoc*, 97, 119–23.

Zhu, X., Conklin, D., Eisenach, J. C. (2003). Cyclooxygenase-1 in the spinal cord plays an important role in postoperative pain. *Pain*, 104, 15–23.

Zuckermann, M., Panconesi, R., Scaricabarozzi, I., Nava, M. L., Bechi, P. (1993). Clinical efficacy and tolerability of nimesulide compared with naproxen in the treatment of post haemorrhoidectomy pain and inflammation. *Drugs*, 46 (Suppl 1), 177–9.



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